UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY
CIVIL ACTION NO 16-MD-2738(FLW)(LHG)

IN RE JOHNSON & JOHNSON POWDER PRODUCTS MARKETING, SALES PRACTICES.	:	DAUBERT HEARING JULY 23, 2019 VOLUME 2

CLARKSON S. FISHER UNITED STATES COURTHOUSE
402 EAST STATE STREET, TRENTON, NJ 08608

B E F O R E: THE HONORABLE FREDA L. WOLFSON, USDJ

A P P E A R A N C E S:

BEASLEY ALLEN, ESQUIRES
BY: P. LEIGH O'DELL, ESQUIRE (ALABAMA)
MARGARET M. THOMPSON, ESQUIRE (ALABAMA)
JENNIFER K. EMMEL, ESQUIRE (ALABAMA)
-and-
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-and-
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BY: JOHN M. RESTAINO, JR., ESQUIRE (CALIFORNIA)
On behalf of Plaintiffs Steering Committee

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(Continued.)

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A P P E A R A N C E S C O N T I N U E D

WEIL GOTSHAL & MANGES, ESQUIRES
BY: ALLISON M. BROWN, ESQUIRE
On behalf of Defendant Johnson & Johnson

SEYFARRTH & SHAW, ESQUIRES
BY: THOMAS L. LOCKE, ESQUIRE (WASHINGTON D.C.)
On Behalf of Defendant Personal Care Products Council

M O R N I N G S E S S I O N

(In open court.)

THE DEPUTY CLERK: All rise.

THE COURT: Thank you.

Everyone may be seated.

Ready to start?

MS. SHARKO: Yes. Thank you, Judge.

Defendant Johnson & Johnson calls Dr. Benjamin G. Neel.

BENJAMIN G. NEEL, called as a witness on behalf of the Defendant, having been first duly sworn, testified as follows:

DIRECT EXAMINATION

BY MS. SHARKO:

Q. Dr. Neel, welcome back to New Jersey.

A. Thank you.

Q. Where did you grow up?

A. I grew up in the Philadelphia area. When I was in eighth grade we moved to Cherry Hill. South Jersey.

Q. What is your job generally?

A. I am the director of the Laura and Isaac

Perlmutter Cancer Center at NYU Langone Health, and I run a 13-person research laboratory at NYU School of Medicine as a Professor of Medicine.

Q. To what has your life been dedicated, Dr. Neel, your professional life?

A. My professional life has been dedicated to the study of cancer, biology, and, more specifically, to understanding cell signalling, which is the mechanism by which cells receive signals from the outside world and how that is abnormal in cancer cell, and more recently, on mechanisms of ovarian cancer pathogenesis.

Q. Now, the Judge has your CV, and it is in evidence, but let's just go through a couple of highlights. I have it on the slides to make it go quicker.

You talked about your current position. Some of the past positions you've had include having a Chair and being a Full Professor of Medicine at Harvard Medical School and being the director of Princess Margaret Hospital Center in Toronto, which is the major cancer center up there. Correct?

A. It's the largest cancer center in Canada.

Q. Does the slide summarize some of your major research interests?

A. Yes.
Q. Now, you have over 200 peer reviewed publications?
A. Yes.
Q. You have been cited more than 45,000 times by the scientific community?
A. Yes.
Q. Does this slide list some of the editorial boards of major journals that you have been involved with?
A. Yes. Including the two most prominent cancer journals currently.
Q. What are those?
A. Cancer Cell and Cancer Discovery.
Q. Does this slide list a few of the honors and awards you've earned as a faculty member?
A. Yes.
Q. Does it include some of your key speaking engagements and meetings that you organized?
A. Yes.
Q. You have done more speeches than the two or three listed on here?
A. Yes. Ms. Sharko, actually, last week I was the keynote speaker at the FASEB Kinase Meeting in Palm Springs; and tomorrow I will be leaving for a major

meeting in Tokyo.
Q. What are the areas of focus for you and your team in the research lab?
A. So about half of my lab works on cell signalling in normal cells and how that is regulated in cancer with a particular focus on tyrosine phosphatase, and the other half works on generating new models of ovarian cancer and the cell of origin of ovarian cancer.
Q. Are you doing anything with the mouse and ovarian cancer currently?
A. Yes. The new models. I should have been more specific, our new mouse models of ovarian cancer. So we basically introduce the same genetic changes that are found in human ovarian cancer. We model them in mouse fallopian tube organoids, and we can study their properties in cell culture and we can take the same cells and inject them in the ovarian bursa and test whether they generate ovarian cancer.
Q. Dr. Neel, has the scientific community's knowledge and understanding of ovarian cancer changed since the time you earned your degrees in the 1980s?
A. Yes. Actually, I tell my students and post docs nothing is the same today as it was when I was their age, and we have actually learned more about cancer

biology in the last 15 years than in all of recorded history before that. We've also learned more I think about the pathogenesis, the molecular pathogenesis of ovarian cancer during that time in the last 15 years than we knew before.

Q. Have you written a report in connection with this litigation?

A. I have.

Q. And the Judge has a copy of your report. It is in evidence. It is also in the binder in front of you.

Are the opinions in your report and your prior testimony and your testimony here today, has all that been expressed or will be expressed to a reasonable degree of scientific and medical probability?

A. Yes.

Q. And are the opinions that you are going to give here today your own?

A. Yes.

Q. What are they derived from?

A. They are derived from my 40 years of experience in the field of cancer biology including 30 years as a faculty member at the institutions that you had on the slide and that are in my CV, and also a review of the relevant literature concerning the topic and a review

of the expert reports of some of our experts and some of the plaintiffs experts and the depositions of some of them.

MS. SHARKO: We'll move on to substantive areas, unless, Judge -- do you have any questions?

THE COURT: No.

BY MS. SHARKO:

Q. Okay. Cancer. Topic One.

Dr. Neel, what is cancer?

A. Cancer is a disease of what we have called the genome, and that's the collection of genes that we have in our body, and it consists of different types of mutations affecting usually six to eight different types of genes that take a normal cell and change it into a cancer cell.

Q. Are there different types of mutations that can occur in a cell to cause cancer?

A. Yes.

Q. What are they and what do they do?

A. As shown on this slide, there are three general categories of mutations that are found in cancer cells and they contribute to cancer: point mutations -- so DNA is like an alphabet, and it's like reading a book. There are different letters, and the precise order of the letters determines the genetic code and also

determines the regulation of the genes that are encoding the genetic code. If you change the letter in a single position -- for example, if you change an A to a T or G to a C, that's a point mutation.

These point mutations can have two different types of consequence. They can cause a gain of function in a protein. They can increase the function of an enzyme, for example, or if they occur in a regulatory sequence, they can increase the expression of a gene of interest.

Alternatively, if they occur in a structural part of a protein, they can cause a loss of function or a decrease in that particular cell activity.

The second general type of mutation is what we call a structural variant, and that involves a change in the structure of chromosomes. That can be, for example, a translocation, and a translocation occurs when chromosomes break and they rejoin inappropriately. For example, the classic example of a translocation is the breakage of chromosomes 9 and 22; and the rejoining of chromosome 9 to 22 to form the Philadelphia chromosome, which causes chronic myelogenous leukemia or CML.

THE COURT: Ms. Sharko, do you have a copy of the PowerPoint?

MS. SHARKO: Yes.

(Pause.)

A. So when the Philadelphia chromosome, for example, is created, that result is in a fusion protein, and in that case a piece of one protein is joined inappropriately to the piece of another protein, and it makes that protein stay on all the time; its activity stays on all the time.

You can also have an inversion which alters the structure of a chromosome. Both translocations and inversions can lead to insertional activation or inactivation of genes.

The third kind of cancer associated abnormality is called a copy number abnormality. A copy number abnormality means an increase or a decrease in the number of copies of a gene or genetic region. Amplification means too many copies, more than the usual number of copies, more than two copies. Deletion means a loss of one or more copies of a gene.

Those are the three major categories of mutations that are associated with cancer.

Q. Now, if a person develops a mutation, does that mean that the person is certain to go on to develop cancer?

A. No.

Q. So in your report at the Bates stamp number pages 9 and 10, you discuss the process of how cancer in general disrupts normal cell regulation. Is this slide and what will follow a fair and accurate representation or summary of how some of the ways in which cancer disrupts normal cell regulation?

A. Yes.

Q. Could you explain that a little please?

A. Sure.

As you can see, on the left-hand part of the slide normal cells have a variety of characteristics. They typically don't grow without growth factor signals. They need certain signals to grow. They also are able to respond to other signals that are called growth inhibitory signals. They self-destruct or undergo, a term you heard yesterday, apoptosis, when they suffer DNA damage that is unrepairable or other types of cellular insults that are unrepairable.

They also divide typically only a limited number of times. They replicate or reproduce their genomes, their genes, with high fidelity. They do not send signals to surrounding blood vessel cells to make new blood vessels, a process known as angiogenesis. They typically are located within a defined region of your body, so a cell in your colon doesn't end up in

your liver.

When normal cells express abnormal proteins, they can display pieces of these abnormal proteins to the immune system and your immune system can eliminate the cells.

Finally, they typically have defining characteristics that make them look unique. A breast cell looks different than a stomach cell, for example. We call this the differentiated state of the cell.

Q. So, now, bring on the mutations, and there are numerous ways that mutations can change cells. Fair to say?

A. Right. The combination of mutations that occur in cancer result in the disruption of all of the processes that I listed on the left-hand part of the slide and just discussed and results in transformation to a cancer cell.

Q. Now, reactive oxygen species commonly known as ROS, what are they?

A. Cells have processes that are normal that generate oxygen or nitrogen radicals. For example, cells, when they respond to certain growth factors, generate hydrogen peroxide, which is one example of a reactive oxygen species. Your mitochondria, which are part of your cells that carry out respiration and

generate energy, they also generate reactive oxygen species as part of normal metabolism. So ROS are produced normally in cells. Also, under certain disease conditions or stress conditions, there can be excess ROS produced. So you can have both normal ROS production and abnormal ROS production in cells. That's what reactive species are.

Q. Is the generation of reactive oxygen species necessarily or always a bad development for the human body?

A. No. As I just tried to explain, part of normal cellular physiology is the production of reactive oxygen species. Cell signalling is impaired in certain cases if you block the production of reactive oxygen.

Q. We have been using the term "cancer" a lot this morning. Is cancer one single disease?

A. No. Actually, one of the major advances in the last 20 years has been the sequencing of, first, the normal human genome, and multiple different types of cancer cells, and that's told us cancer is actually many different types of diseases caused by many different types of mutations such as I've already discussed occurring in different cells of origin. So cancer has many diseases.

Q. Let's now switch topics and go to ovarian cancer. Is ovarian cancer a single disease?
A. No.
Q. What are the different types of ovarian cancer?
A. So, again, this is also information that has become available over the last -- more available over the last 15 to 20 years. And there is nonepithelial ovarian cancer, and epithelial ovarian cancer. As I understand it, the subject of this litigation is epithelial ovarian cancer. So I won't discuss the non-epithelial forms, and these forms account for 90 percent of ovarian cancer anyway.

THE COURT: Which accounts for 90 percent?

THE WITNESS: Epithelial ovarian cancers. So the epithelial ovarian cancers have been subdivided into two large subcategories: Type I tumors, as you can see on the slide, and these are low grade serous ovarian cancer, mucinous carcinoma, endometrioid, and clear cell carcinoma.

Q. So do these two types of tumors have different cells of origin and different genetic mutations that lead to them?
A. Yes. You can see on the slide the cell of origin of Type I tumors are often from endometriosis or endometriotic lesions that come from the

endometrium in the uterus and are transplanted to the peritoneum, and the mutations that cause Type I tumors, as you can see from the slide, are generally point mutations in genes that are involved in cellular signalling or epigenetic regulation.

Q. Let's go to Type II cancers or Type II tumors.

A. The Type II tumors are mainly serous high grade, serous ovarian carcinoma, and its relatives. These are all very similar types of tumors, and one of the major discoveries in the last 15 years has been that at least 60 percent of high grade serous ovarian cancers originate in the fimbriae of the fallopian tube. And unlike the Type I tumors high grade serous ovarian cancer or Type II tumors is a copy number and structural variant disease. Its hallmark is genetic or genomic instability.

So if I can summarize, the Type I and Type II tumors originate in different cells of origin, and they are caused by different mutations, and they are caused by different mutagenic or mutational processes.

Q. I see on the slide under Type II tumors TP53 in several boxes, but I don't see that for Type I tumors.

First of all, what is TP53 or a p53 mutation?

A. Scientists have a nomenclature. So TP53 is the official human gene name for the gene that encodes a

protein called p53. Most of us refer to it as p53, but the official gene name is TP53, and p53 is a particularly important gene in cancer.

Q. Why?

A. P53 is a hallmark tumor suppressor gene. As I said earlier, there are a gain of function mutations and loss of function mutations in different cancers. Gain of function mutations occur in genes that we call oncogenes. And the loss of function mutations occur in the other kind of cancer-associated gene tumor suppressor genes. P53 is the hallmark tumor suppressor gene and at this time has many important functions in maintaining cell integrity.

Q. What is the p53 relationship to the causation of ovarian cancer?

A. The Type II tumors essentially all have either a point mutation followed by a deletion in p53 or they have loss of both copies of p53. So p53 mutation or deletion or both is sort of the sine qua non of Type II tumors, and it's also the earliest event in the Type II tumors.

Q. Dr. Neel, do you have an opinion to a reasonable degree of scientific and medical probability as to whether talc exposure causes p53 or any other gene mutation?

A. Yes.
Q. What is your opinion?
A. There is no evidence to support that claim.
Q. Now, in your expert opinion as a cancer biologist, what is the significance of epidemiologic studies that lump together all the ovarian cancer subtypes?
A. I would view them with some skepticism.
Q. Why?
A. Because as the slide indicates, these tumors are caused in different cells of origin by different types of mutations, and, generally, mutagenic agents cause different types of mutational processes. They don't cause multiple types of mutational processes such as the case for the Type I tumors versus the Type II tumors.
Q. Now, let's turn to another one of the plaintiffs' hypotheses.

What are MUC-1 antibodies?

A. MUC-1 is a mucus glycoprotein that is expressed on fallopian tube cells and other cells, and antibodies against MUC-1 would be antibodies directed against that glycoprotein, directed against MUC-1.
Q. Dr. Neel, do you have an opinion to a reasonable degree of medical and scientific probability as to

whether the use of talcum powder products increases the risk of ovarian cancer or causes ovarian cancer by prohibiting MUC-1 antibodies as hypothesized by the plaintiffs' experts?

A. Yes.

Q. What is your opinion?

A. There is no evidence to support that claim.

Q. Okay. Let's turn to biologic plausibility.

MS. SHARKO: Judge, there are more details in his report on some of his opinions, but to save time, we're just covering the highlights.

THE COURT: I understand.

Q. Biologic plausibility, what is it?

A. Biologic plausibility means to me that there is some experimental evidence to support a hypothesis about a potential cause of a cancer.

Q. Why is that important particularly in a case like this?

A. It's particularly important when the other evidence is relatively inconsistent or weak. For example, when the epidemiological evidence is in conflict and/or the purported effect size of a particular agent is small or relatively small, it's particularly important to have some sort of scientific evidence as to the mechanism by which a particular

agent would be proposed to cause the cancer.
Q. When you are reviewing papers for scientific journals, is biologic plausibility something you look for?
A. Actually, it's everything I look for along with technical credibility. In fact, every paper that I publish is designed to test the biological plausibility of a hypothesis.
Q. Is biologic plausibility also one of the several Bradford Hill criteria?
A. Yes, it is.
Q. Do you need absolute proof of mechanism to have biologic plausibility?
A. No, but you need to have some credible scientific evidence supporting the hypothesis.
Q. Why do you need more than just a hypothesis to show biologic plausibility?
A. A hypothesis without evidence is basically an opinion or speculation.
Q. In your opinion, to a reasonable degree of medical and scientific probability, is it biologically plausible that the perineal application of talcum powder products causes ovarian cancer?
A. No, not with the present evidence.
Q. Now, what does our current understanding of Type

I and Type II tumors tell us about whether the plaintiffs' theory here is biologically plausible?

A. It's unlikely a single agent would cause both types of tumors because, as I said earlier, both types of tumors initiate in different cells of origin and have different mutagenic processes underlying them. It's also unlikely an agent that has never been shown to be mutagenic would cause these mutations.

Q. We talked about biologic plausibility. Let's go to causation.

Do you have an opinion to a reasonable degree of scientific and medical probability as to whether the perineal use of talcum powder products cause ovarian cancer?

A. Yes.

Q. And what is your opinion?

A. There is no evidence to support that claim.

Q. Now, moving along. Next would be migration. We'll skip over that in deference to other experts so we don't have repetition, and let's go to inflammation.

Do ovarian tumors have inflammation associated with them in general?

A. Fully blown ovarian cancers -- so if a woman has a fully blown ovarian cancer, those tumors are

associated with inflammation. Interestingly, those tumors are associated with different types of inflammation. For example, one woman's tumor could be associated with different types of inflammation than another woman's tumor. This is tumor-associated information. So ovarian tumors are associated with inflammation.

Q. Does that mean the inflammation caused the ovarian cancer?

A. No. In order to understand or to study whether inflammation causes ovarian cancer, you have to look at the early events in ovarian cancer and ask whether there is any evidence that the early events are associated with inflammation.

Q. So what are precursor lesions? Is that the earlier events you are talking about?

A. Yes. So precursor lesions are lesions you can see under a microscope either with standard stains or sometimes with specialized immunohistochemical stains. These lesions have been shown by molecular approaches to be the cells that give rise to the eventual fully blown ovarian cancer. So that's what a precursor lesion is.

Q. What are STICs?

A. STICs stands for serous tubal intraepithelial

carcinoma, and STICs are the hallmark of preneoplastic or precursor lesion of high grade serous ovarian cancer. They are an example of a precursor lesion for high grade serous ovarian cancer.

Q. What is a p53 signature?

A. So p53 signature is thought to be potentially an earlier precursor lesion. So p53 signature means a cluster of cells that stains with an antibody directed against p53, and many times the p53 mutations result in an abnormally stable form of the protein, and that means that it can be detected by an antibody. Typically p53 is very unstable and it doesn't stain well with antibodies.

So a p53 lesion can indicate an even earlier tumor but it is not as strongly associated as a STIC.

Q. Are precursor lesions, STICs, and p53 signatures associated with chronic inflammation?

A. Not as far as I'm aware, no.

Q. Why is that important?

A. Well, because, as I just said, if you want to adduce a particular -- an agent as causing a particular condition, you should be able to see that that process or agent is present in the precursor lesion because that's where the tumor is being formed.

Q. Have people actually looked at STICs under the

microscope to see if they are associated with chronic inflammation?

A. Yes.

Q. Who has done that, which scientists?

A. A study by Malmberg looked at STICs from normal patients and patients undergoing risk reduction surgery for BRCA1 and BRCA2 lesions and found no evidence of increased inflammation.

A second study by Dr. Shih, which is unpublished but I reviewed, showed similar findings.

THE COURT: When was the other study done, by Malberg, the earlier one you mentioned, when was that?

THE WITNESS: The date, I can look that up. It is cited in my report. 2016.

MS. SHARKO: Malmberg is Exhibit A 91 to the Tersigni certification, and it was published in 2016.

THE COURT: Thank you.

Q. Dr. Shih's paper is in the notebook of exhibits and it starts in his expert report around page 25.

Who is Dr. Shih?

A. He is one of the world's prominent and respected gynecological pathologists, and he is a professor at Johns Hopkins Medical School.

Q. Would it be accurate to classify Dr. Shih's work as a mere hypothesis?

A. No.
Q. Why not?
A. He actually posed a hypothesis as part of his report and he tested that hypothesis by examining a number of specimens, and that would be an experiment. So it is not a hypothesis.
Q. Now, after you wrote and submitted your expert report, did you have access to Dr. Shih's study?
A. Yes.
Q. Did you review it as critically as you would if you were peer reviewing a paper for one of your journals?
A. Yes.
Q. What conclusions did Dr. Shih reach regarding STICs and chronic inflammation?
A. He found no evidence for an antecedent inflammation in these lesions.
Q. What does all of this evidence tell us about chronic inflammation and ovarian cancer pathogenesis?
A. It means that although several authors have suggested chronic inflammation might play a role in ovarian cancer, that remains a hypothesis and basically speculation at this point.
Q. Switching topics.
Asbestos. Plaintiffs claim that the products

are contaminated with some amount of asbestos which we deny. But if the defendants' talcum powder products are shown to contain asbestos, would that matter to your analysis, findings, and conclusions?

A. No.

Q. Why not?

MR. RESTAINO: Your Honor, I object. Dr. Neel did not go into asbestos in his expert report. When he was asked during his deposition about his opinions regarding asbestos and ovarian cancer, he said, I have no opinion in this regard, and we didn't go any further into that based upon his opinions.

MS. SHARKO: It is not a problem because I only have one final question in this area, and it is exactly what he was asked and testified in his deposition.

THE COURT: Let me hear the question.

Don't answer.

BY MS. SHARKO:

Q. I think the question was -- he said that it wouldn't matter, and I asked, why not?

THE COURT: I guess the question is: Was that asked in the deposition and explored?

MS. SHARKO: What I expect Dr. Neel is going to say is exactly what he said at his deposition at

page 49:19 --

THE COURT: The issue was whether it was explored in his deposition?

MS. SHARKO: Yes, it was.

THE COURT: Okay. Proceed.

Do you have the question?

THE WITNESS: Yes.

I was asked my understanding of my role in this litigation, was to offer comments as to the biological plausibility of talc products or talc in ovarian cancer, and, therefore, I reviewed the literature concerning that topic, and whatever was used in that literature is what the plaintiffs are alleging is the evidence in favor of biological plausibility. So, no, it wouldn't matter what was in them because I found no evidence supporting that claim.

BY MS. SHARKO:

Q. Now, last big topic.

Dr. Saed, have you reviewed the expert report, depositions, lab notebooks, peer reviews, drafts and manuscripts of Dr. Saed?

A. Yes.

Q. Do you have an opinion to a reasonable degree of medical and scientific probability on the methodology

that Dr. Saed used in coming to his opinions?
A. Yes.
Q. And what is your opinion?
A. It's seriously flawed on multiple levels.
Q. Does the data that Dr. Saed reports from his experiment support the conclusion that exposure to Johnson & Johnson's talcum powder products can cause ovarian cancer?
A. No. And in my opinion they don't even address that question.
Q. Now, your report, the reports of Dr. Boyd, Dr. Shih, and Dr. Mossman, all critique Dr. Saed's experiment at length, and the Judge has those. So I'm going to cover a couple of the specific methodological criticisms outlined in your report, but we're not going to do everything.

What are SNPs?

A. SNPs are single nucleotide polymorphisms. So SNPs are actually normal variants that are present in all of us. If we compare my DNA to your DNA, or to the Judge's DNA, we will have a variation on average every 300 bases, and those variants are called SNPs. Most SNPs have no biological consequence. They represent the normal variation we have between all of us in our courtroom.

SNPs are useful in science because they can be used to map genes, and some SNPs are actually deleterious and associated with disease.

Q. What do we know about these risk conferring SNPs?

A. We know that large-scaled genetic association studies called GWAS or genome-wide association studies. So we know that large scale genetic association studies or GWAS have mapped a number of SNPs that are associated with risk of ovarian cancer.

Q. Where do I find this GWAS thing?

A. You can go to any browser and type in GWAS catalog, and it will take you to the website; and when you get to that website, you can put in any SNP or you could put in any gene that has SNPs in it which all genes do, or you can put in a disease like ovarian cancer and it will list all the SNPs associated with the disease to statistical significance.

Q. About how many SNPs are associated with an increased risk of ovarian cancer?

A. The last time I did the analysis was around the time of my deposition, and I went to GWAS catalog and there are about 100 SNPs that have been associated to varying degrees of statistical relevance with ovarian cancer.

Another important point about SNPs is because when you look at SNPs, the way these studies work, they look at all of the SNPs at once. So there is a statistical problem of multiple comparisons. So in order to associate a given SNP with a disease, you have to have a high statistical relevance. So only ones that are statistically significant to a P value of 10 to the minus 8 or less are statistically significant. That's how you interpret the data on GWAS.

Q. Doctor, did Dr. Saed study in his experiments any of those SNPs that are associated with ovarian cancer according to the GWAS compendium?

A. As far as I'm aware at the time I last checked none of the SNPs that Dr. Saed studied in any of his publications or for his deposition or expert report have been linked conclusively to ovarian cancer generation while many others have been.

Q. Now, do you have an opinion to a reasonable degree of medical and scientific probability as to whether talc can cause the specific changes in specific SNPs that Dr. Saed believes it can?

A. Yes.

Q. And what is that opinion?

A. It is completely inconsonant with everything we

know about modern molecular biology.
Q. Why?
A. Well, I think it is easier to understand if I explain how true mutagens work. A typical real carcinogen or mutagen like benzopyrene or X-rays or UV randomly introduce DNA damage into cells. So if you have a plate of cells and you expose the cells to a mutagen, there will be DNA damage, and some of that DNA damage won't be repaired if you have enough mutagen and you will get mutations, but those mutations will be random. Then when you mutate a gene, that provides a selective advantage to the cell over time but not 48 or 72 hours, that clone of cells will grow out, and you will see the mutation. But it is impossible, as far as we know, for any substance to quantitatively convert a particular locus to another code within 48 to 72 hours, as Dr. Saed alleges, and even more incredible to allege that multiple SNPs are changed during that time period. It simply is not credible.
Q. Can any substance do that that you are aware of?
A. Not that I'm aware of. In fact, even our most modern engineering technologies like CRISPR /CAS technology would not be able to do that. It would be difficult to do with that technology.

Q. Let's go to animal studies. Is Dr. Saed's experiment validated by animal studies?
A. No. As far as I know, he didn't do any animal studies.
Q. Why is animal testing important when you go from in vitro or the lab to in vivo or humans?
A. Well, the standard in the field to assess whether a cell is a cancer cell is to see whether it can form a tumor. There are examples of cells that behave in a semi-transformed way in cellular assays but do not form tumors, and they are not fully developed cancer cells or can't be shown to be fully developed cancer cells. So it is essential -- if you are going to assert something is a cancer cell you have to test it as its tumor-forming capability.
Q. What do the animal studies show with regard to talc and ovarian cancer, limiting your answer to the studies you discussed in your report.
A. There is no evidence there is any neoplastic or preneoplastic changes caused by introduction of talc either directly into the ovarian bursa or on the perineum.
Q. Let's go now to lab notebooks. Did you review Dr. Saed's lab notebooks?
A. I did.

Q. Why are lab notebooks created?
A. Because it is essential to create a contemporaneous record of the hypothesis that's being tested, the procedures that are being carried out to test that hypothesis, the results that are obtained and usually the provisional interpretation of those results.
Q. Why is that important?
A. Because in order for science to be replicated. You have to know what the experimentalist did.
Q. What did you tell your grad students about this?
A. Well, it's a little flippant. What I usually tell them is that it is critical to keep good laboratory notebooks because if they go outside and get hit by a truck, after we're finished mourning them, we want to be able to get on with their work.
Q. Now, what did your review of Dr. Saed's lab notebooks and other materials tell you about his laboratory practices?
A. They are irregular at best and sloppy at worst.
Q. Is it acceptable to use white-out in a lab notebook?
A. No. I've never seen anyone use white-out in my 30 years as a faculty member.
Q. Dr. Neel, what does it mean to do an experiment

in triplicate?

A. This is complicated. In general science requires replicates or replications, and there are two different types of replicate -- biological replicates and technical replicates. Biological replicates means you take the same cells, you plate them on day one and you expose them to some sort of a stimulus or agent; and you read out a result, and you do the same thing on days two and three.

Biological replicates are important to rule out the typical biological variability that occurs between cells.

Technical replicates means you do the same assay in multiple times, and that has to do with the precision of the assay measurement.

So, typically, experiments are done with both biological and technical replicates.

Q. Let's go to cell lines. Did Dr. Saed test the correct cell lines in his experiment in your opinion?

A. In almost all cases, no.

Q. For example, SKOV-3 what is the significance of testing that to you?

A. I think the choice of SKOV-3, for example, is inapt in two different ways. The first way is Dr. Saed was investigating whether talc had effects on

the initiation or the causation of ovarian cancer. SKOV-3 is already an ovarian cancer cell. So you really can't learn much about whether something is causing a cancer by testing something that is already a cancer.

Secondly, SKOV-3 is not a high grade serous ovarian cancer cell line. As I understand the contention of the plaintiffs, there are major claims on serous ovarian cancer.

Q. Let's go to oxidative stress and transformation. Plaintiffs claim the papers by Buz'Zard and Shukla are supportive of Dr. Saed's data and conclusions. Are they consistent with Dr. Saed's data and conclusions?

A. No.

Q. Let's start with the Buz'Zard paper. What is not consistent there?

A. If you actually look -- so one of Dr. Saed's claims is that you could measure oxidative stress simply by measuring the levels of the RNA or protein for pro and/or antioxidant enzymes. I contend in my report and testify now that it is essential to actually measure reactive oxygen species in the same cells.

In the Buz'Zard paper they used the same dose of talc as Dr. Saed did and actually found ROS levels

were actually lower in the treated cells than in the controlled cells, and Dr. Saed claims that ROS would be higher. So I think that is definitely inconsistent.

The second inconsistency is that the effects of proliferation which Dr. Saed claims were also not seen by Buz'Zard at the same dose of talc.

Q. What is gene expression?

A. As you know, we have multiple genes, and at any given time, many of them are making RNA and that's called gene expression. They are making messenger RNA, and that's called gene expression. You can measure that by doing today something called RNA sequencing, or RNA-seq for short, and previously you could do that by using Affymetrix arrays. That's what gene expression is.

Q. Dr. Shukla's experiment as reported in her paper found no changes in gene expression in cells exposed to talc. Correct?

A. That's correct.

Q. Why is that significant?

A. Because if you don't significantly affect gene express, that essentially means a substance is biologically inert in that cell type.

Q. Plaintiffs and Dr. Saed claim talc is

pro-oxidative and that ovarian cancer is associated with oxidative stress. What is oxidative stress?

A. Oxidative stress is when reactive levels of reactive oxygen species exceed the level of antioxidants in cells. So there is an excess of ROS.

Q. Dr. Neel, is it generally accepted in the scientific and medical community that oxidative stress causes ovarian cancer?

A. No. That's one of the hypotheses that exists, but it is not in any way accepted.

Q. Is it generally accepted in the scientific and medical community that oxidative stress plays a role in the pathogenesis of ovarian cancer?

A. No.

Q. Do Dr. Saed's data even establish that talc increases oxidative stress?

A. No.

Q. Do the data that Dr. Saed reports from his experiment support the conclusion that inflammation or oxidative stress are relevant to ovarian carcinogenesis?

A. No. In fact, in my opinion, the experiments he did can't even address that question.

Q. Let's go to CA-125, which Dr. Saed said was a hallmark of ovarian cancer.

First of all, what is CA-125?
A. CA-125 is what we call a biomarker of ovarian cancer. It's basically used by physicians to monitor the level of ovarian cancer cells in a woman's body who has ovarian cancer.
Q. Is it a hallmark of ovarian cancer?
A. Not insofar as hallmark means that it is involved in the causation of the ovarian cancer. There is no evidence to support that.
Q. Let's go to peer review. Did you review the Gynecologic Oncology peer review comments on Dr. Saed's manuscript?
A. Yes.
Q. What are your opinions as to those comments?
A. I agree with those criticisms.
Q. Are all peer review processes created equal?
A. No.
Q. What kind of peer reviews are given for an abstract or a poster in your experience?
A. Having led many meetings, both national and international, I'm very familiar with what happens with poster reviews. What happens is the authors or the applicants to the meeting submit an abstract. That's all they submit. They don't submit any data. They just submit the abstract. And then a decision is

made as to whether to give a poster presentation or a talk.

The most interesting and most provocative papers or abstracts, sorry, are given public oral publications and the less interesting ones are given posters.

Q. When it was asserted yesterday that 20 to 25 people peer reviewed Dr. Saed's paper before it was published, what does that mean to you as a scientist with over 200 peer reviewed publications and the editor of six journals?

A. I think that's a highly misleading assertion.

Q. Okay. In summary, last topic, let's turn to the relevance of what Dr. Saed did.

Do you have an opinion to a reasonable degree of medical and scientific probability as to Dr. Saed's study, including the conclusions that he draws, has any relevance to the cause of human ovarian cancer?

A. Not in my opinion, no.

Q. Is it justifiable in your opinion from a scientific point of view to extrapolate from Dr. Saed's work to the cause of ovarian cancer in humans?

A. No.

Q. Dr. Neel, are there good grounds for Dr. Saed's

opinions?
A. Not in my opinion, no.
Q. Do Dr. Saed's conclusions flow from facts known to scientists or the methodology that Dr. Saed employed?
A. No. As I've indicated, some of his conclusions are completely inconsistent with modern molecular biology.
Q. Does Dr. Saed's experiment tell us anything at all about how talc behaves in the real world of the female reproductive system?
A. No.
MS. SHARKO: Thank you very much.
Judge, I'm finished unless you have any questions.
THE COURT: No. Thank you.
Plaintiffs want a few moments before you start?
MS. O'DELL: Yes, please.
THE DEPUTY CLERK: All rise.
(Recess.)
(Continued on the next page.)
///

THE DEPUTY CLERK: All rise.

THE COURT: Thank you.

BENJAMIN G. NEEL, resumed.

CROSS-EXAMINATION

BY MR. RESTAINO:

Q. Good morning, Dr. Neel. My name is John Restaino. We had the brief privilege of meeting each other during your deposition in New York. I have some questions that I prepared and some questions based upon your testimony this morning.

No. 1, first, it would be helpful for us to establish the standard by which you wrote your expert report and you based the opinions therein, because I heard multiple times today your opinion was based on a reasonable basis of scientific probability. Does that sound familiar?

A. I don't recall exactly. I don't recall saying that.

Q. Well, you were asked if your opinions were held to a reasonable degree of medical certainty or medical probability. Do you remember that?

A. Yes.

Q. That's not what you testified in your

deposition, did you, sir?

A. I probably testified to what I was asked.

Q. Let's look at what you testified as to the standard you employed in developing your opinions and writing your expert report.

For example, on the Bradford Hill viewpoints, you are familiar with them?

A. Yes.

Q. You reviewed the Bradford Hill viewpoints in preparation for writing your expert report. Right?

A. Yes.

Q. It was reference 5 in your expert report. And you were asked at your deposition on page 153, 23 --

A. I don't have that deposition. Do I? Do I have it?

THE COURT: Is it in the binder you gave to me?

MR. RESTAINO: Page 153, 23, to page 154, 1.

MS. SHARKO: I object. I don't see how this goes to the questions he was asked.

THE COURT: I think we're looking at different things. You are asking him generally what is the standard, and we know what the standard is under Daubert and how opinions should be held. Now, you are asking specifically about Bradford Hill. I think it's

a bit of a disconnect, but feel free to ask him about Bradford Hill.

BY MR. RESTAINO:

Q. In fact, throughout your deposition it was your opinion the evidence must be compelling. Correct?

A. Yes.

Q. Definitive?

A. Well, I think it probably would depend on the context of the exact question when I said "definitive."

THE COURT: There is a difference between his opinions, and we're looking at something different here. Keep going.

Q. In order to have an argument in favor of biological plausibility, do you have an opinion whether or not the evidence must be compelling and definitive?

A. I understand where the concern is. The evidence itself has to be compelling and definitive, but it doesn't mean the evidence covers everything. The evidence produced has to be compelling and definitive. Is that helpful?

Q. Doctor, you are a cancer biologist. Correct?

A. Yes.

Q. An MD and Ph.D.?

A. Yes.
Q. When is the last time you actually examined a patient?
A. 1988.
Q. Would that be the last time you examined the genitals of a female?
A. Yes.
Q. You are not an oncologist actively treating patients with cancer. Correct?
A. Correct.
Q. Doctor, you are a cancer biologist that works in a laboratory. Correct?
A. I work in a laboratory for part of my time, and the rest of my time I run the Perlmutter Cancer Center at NYU Langone, and in that capacity I'm responsible for the entire cancer service line and all cancer research at NYU Langone Health.
Q. That's more of a role as an administrator. Correct?
A. Yes.
Q. But in the laboratory you conduct research involving cancer biology?
A. I oversee the research. I don't do many experiments anymore. My post docs would think that is a bad thing.

Q. Have you or the individuals you oversee ever conducted a study looking at the molecular effects of talc?
A. No.
Q. Now, in preparing your opinions for this case and your expert report, it is true one of the methodologies you employed was an online search using search engines such as Google and PubMed?
A. Yes.
Q. And you developed keywords to conduct that search . Correct?
A. Yes.
Q. Two of the key words you utilized were "ovarian" and "cancer." Correct?
A. Yes.
Q. And another one was "inflammation." Correct?
A. Yes.
Q. On PubMed, if one types in "ovarian cancer," then a list of a lot of articles are going to come up that either have "ovarian cancer" in their title or "ovarian cancer" in the corpus of the article. Correct?
A. Yes. I didn't just do "ovarian cancer." I did "ovarian cancer" and various questions because, obviously, "ovarian cancer" would be very large, just

to clarify.

Q. And you also searched for "inflammation"?

A. In the context of "ovarian cancer." So it would be "ovarian cancer" and "inflammation." It's been a long time, so I don't remember exactly everything I searched, to be honest.

Q. Once the list of articles came up on the screen in PubMed -- last night, when I ran a search using "ovarian cancer," "talc" and "inflammation," there were 1,122 articles that came up. Then you scanned those articles that were germane to your opinions. Correct?

A. Yes.

Q. Some you selected and some you did not select. Correct?

A. Yes. I looked at the abstracts for most of them, as I recall.

Q. And from those abstracts you then selected articles that you would review in full. Right?

A. Correct. Mostly focused on the more recent data.

Q. Now, once you saw the abstracts -- looking at "talc" and "inflammation," there are articles written and published that come down on the side of talc causing inflammation and talc not causing

inflammation. Is that correct?
A. Yes.
Can I expound on that? Some people would consider granulomas to be inflammation. So there is no that question talc causes granulomas. The issue I was looking for when I prepared my expert report was whether talc caused the kind of inflammation that is associated with cancer or cancer initiation. That was the focus of my expert report.
Q. Granuloma formation is one of the results of the body's immune system reacting to, for example, a foreign body. Correct?
A. That's correct.
Q. That is an inflammatory reaction?
A. Again, to clarify, granulomas are not associated with ovarian cancer development. Inflammation is a broad term, as you know, and it is important to focus on the key aspects when you are trying to investigate a subject.
Q. However, for clarification, inflammation would be the first step in acute foreign body reaction inflammation which then can in some cases go on to cause chronic inflammation, which has been caused with cancer formation or the body may form a granuloma to wall that foreign body or splinter one might get

walking on the boardwalk?
A. I think it is much more complicated than you are making it.
Q. There are specific cells we have within our body that are part of the innate immune system. Correct?
A. That's correct.
Q. These would include macrophages?
A. Correct.
Q. Lymphocytes?
A. Lymphocytes are part of the adaptive immune system and not the innate immune system.
Q. Can you explain that?
A. Macrophages are part of the innate immune system. These are the official cells that respond to invaders like infections, and then they trigger the production of cytokines and chemokines which can lead to the engagement of the innate immune system. Lymphocytes are part of the innate immune system.
Q. What other cells in addition to the lymphocytes would you expect to find within the innate system?
A. As I just said, lymphocytes are not part of the innate system.
Q. I'm sorry. The adaptive.
THE COURT: I want to be clear. Lymphocytes are part of --

A. (Continuing) -- lymphocytes are the sine qua non of the adaptive immune system. Innate and adaptive. Lymphocytes -- there are two major classes of lymphocytes. T lymphocytes and B lymphocytes. T lymphocytes mediate cell immunity and B lymphocytes produce antibodies. They are the adaptive immune system.

Q. Are there other cells that are listed or can overlap with the adaptive system?

A. If you are taking about NK cells, most people would classify them as innate. They are sort of an overlap category. It stands for natural killer cells.

Q. The presence of NK cells can suggest chronic inflammation. Correct?

A. Yes.

Q. The presence of lymphocytes can indicate chronic inflammation?

A. Yes.

Q. The presence of macrophages can indicate chronic inflammation?

A. Yes.

Q. Doctor, according to your expert report, you published 234 peer-reviewed manuscripts. I'm assuming since the time you filled this out, there are probably more?

A. I think this was pretty up to date. There may be one more.
Q. You also published 33 invited review articles. Correct?
A. Correct.
Q. We heard yesterday from Dr. Saed that an invited review article involves an individual who is recognized by a journal, by a journal editor, whatever the case may be, to be an expert in that area and asked to write a review of the literature germane to that particular topic of which the person is an expert. Right?
A. It is a little bit more complicated than that. I guess I would have to say no because it is a little more complicated than that.
Q. Are you aware of any situation where a review article has been written by someone who was not an expert in that field?
A. Yes.
Q. Have you ever written a review article on an area in which you do not hold expertise?
A. I try not to.
Q. So you have not?
A. No.
Q. Have you ever written a review article looking

at the inflammatory effects of talcum powder?
A. No, I haven't.
Q. Have you ever written a review article looking at the inflammatory aspects of involving premalignant ovarian cancer?
A. No.
Q. In your review of the abstracts and then articles that you have selected to review for your opinions, did you see abstracts and articles that were contrary to your opinions?
A. On the surface, yes.
Q. Did you read those in addition to those that supported your opinions?
A. Of course.
Q. How did you go about weighing which article would be utilized in your expert report? For example, the con and the pro, what was the methodology you used to weigh those?
A. The same methodology I would use to write any review article for the scientific literature. If I thought the topic was on point, then I would definitely include. If I thought the topic was not, I wouldn't include it.
Q. If the topic was on point and the conclusion was long-term genital exposure to talc resulted in an

increased risk of ovarian cancer, would you include that?

A. Yes.

Q. You testified of your 234 peer-reviewed manuscripts you have been cited 45,000 times. Correct?

A. That was at the time of submission of my CV, yes. It may be a little higher now.

Q. Why did you share that information with the Court?

A. I think it speaks to the level of impact that I have in the field and my expertise along with my H index.

THE COURT: What is that?

THE WITNESS: The H index is the number of papers you have that have been cited that number of times. So 107 papers cited at least 107 times.

Q. You consider the H index to be indicative of general acceptance of your work?

A. I think all metrics are imperfect, but the H index is thought to be along with the i10 and several other metrics you can use them together to sort of assess expertise, yes.

Q. A reader seeing your work and noticing an H index of what is probably 107 would then consider your

work to be at least worthy of reading. Would you not agree?

A. Yes, in general.

Can I clarify?

Q. Of course.

A. Generally, readers of papers don't necessarily look at H indices to evaluate that. People in the field know the names of people in the field.

Q. Your time at Harvard, do you know Dr. Graham Colditz? He is a physician epidemiologist?

A. I believe he is at Washington University, St. Louis.

Q. Are you familiar with Dr. Graham Colditz's work looking at talc and ovarian cancer?

A. He is an epidemiologist. So if he was involved in the epidemiological study I read, then, yes. I don't remember all the authors on the papers, frankly.

Q. Did you read an expert report written by Dr. Graham Colditz in talc litigation?

A. I did not.

Q. Do you know that Doctor Graham Colditz has concluded long-term genital to talc has resulted in an increased risk of ovarian cancer?

MS. SHARKO: I object. Dr. Colditz is not an expert in this particular case. No expert report was

served by him.

THE COURT: Mr. Restaino.

BY MR. RESTAINO:

Q. When you were doing your PubMed search for ovarian cancer, did you see the publications by Dr. Graham Colditz?

A. As I just indicated, Mr. Restaino, I reviewed a large number of epidemiological studies and I don't recall who was the author on all of those studies. I remember some of the names but not all of them, but I do remember a large number of epidemiological studies. I don't remember the authors, all of the authors on each of those studies and the most recent meta-analyses.

Q. In looking at the various epidemiological studies that you did review, did you pull those studies that found an association in addition to those that did not?

A. Yes.

Q. Do you know what Dr. Graham Colditz's H index is?

A. I'm sure it is quite high.

Q. If I represent to you Dr. Colditz is the No. 2 cited author in the world with an H index of 287, would that surprise you?

A. No.

MS. SHARKO: Objection. Relevance.

THE COURT: He's answered it.

Move on.

BY MR. RESTAINO:

Q. Doctor, you were asked about ROS reactive oxygen species?

A. Yes.

Q. Anything that leads to increased inflammation can lead to an increased production of reactive oxygen species. Correct?

A. There are two conditionals there. Can you simplify that question.

Q. Let me reask the question.

It is true anything that leads to increased inflammation can result in increased production of ROS?

A. If the answer is, is it possible? Yes.

Q. Is it more likely than not?

A. That anything that causes chronic inflammation -- anything that causes chronic inflammation where there is macrophages and neutrophils in the environment, if they are chronically stimulated, they can produce excess reactive oxygen species, yes, not lymphocytes.

Q. You just mentioned a cell type that hadn't been mentioned previously, and that's neutrophils.
A. I mentioned that earlier.
Q. Are neutrophils part of the adaptive or innate system?
A. Innate. Innate is classically defined as macrophages and neutrophils.
Q. When there is an inflammatory process, there is not, for lack of a better word, barrier that prevents the macrophages, neutrophils from co-mingling with lymphocytes. Correct?
A. Sometimes. It depends on the type of inflammation, what is in the inflammatory microenvironment.
Q. Do you agree that reactive oxygen species have the potential to damage DNA and lead to mutations under certain conditions?
A. Yes.
Q. In fact, if we can bring up on the slide your expert report, page 8, in the first full paragraph. You wrote agents or conditions that lead to increased inflammation can result in the production of reactive oxygen species ROS which can damage DNA and lead to mutations under the certain conditions?
That's your opinion. Correct?

A. Yes.
Q. You will agree any agent that promotes especially chronic inflammation can result in increase ROS formation?
A. It is possible.
Q. Is it more likely than not that it is going to occur?
A. It depends on the type of inflammation.
Q. And that increased ROS development can result in mutagenesis?
A. Yes. And that can be tested for.
Q. Now, associated with reactive oxygen species is also oxidative stress. Correct?
A. That's not exactly correct.
Q. Isn't oxidative stress produced by an imbalance between ROS production and the body's ability to detoxify those?
A. That's an accurate statement.
Q. Would you agree that oxidative stress is generally accepted as a critical path though physiological mechanism in different human pathologies including cancer?
A. Can you repeat the question.
Q. It is generally accepted that oxidative stress is a critical pathophysiological mechanism in

different frequent human pathologies which can include cancer?

A. Yes. But not all. Just so I'm clear on the question, because it had a lot of modifiers.

Q. ROS can cause protein damage?

A. Yes.

Q. ROS can cause lipid damage?

A. Excess ROS.

Q. Thank you for saying that because you testified that this is also a normal process?

A. Yes. ROS production is a normal process, yes.

Q. And apoptosis is a normal physiological process?

A. Absolutely.

Q. We are all experiencing apoptosis now by virtue of being alive. Right?

A. Yes.

Q. It's the programmed normal death of a cell?

A. Yes.

Q. Cellular proliferation is a normal cellular process?

A. In some cells, yes.

Q. All of us in the courtroom are undergoing in some of our cells cellular proliferation right now. Right?

A. Yes.

Q. Excess abnormal apoptosis is not normal physiological process. Correct?
A. That's correct.
Q. Excess cellular proliferation is not normal. Correct?
A. Correct.
Q. We all need oxygen here in this room to stay alive. Correct?
A. Yes.
Q. If this room was filled with 100 percent oxygen, we are not going to stay alive very long?
A. That's complicated. What do you mean by "very long."
THE COURT: I think we can move on.
Q. There is a difference between normal physiological responses and abnormal physiological responses even if they are the same thing, for example, as cellular proliferation?
A. Yes.
Q. Now, you agree that different lifestyle and environmental related factors may be pro-carcinogenic?
A. Yes.
Q. All cancer does not develop strictly because of genetic abnormalities?
A. That's incorrect. All cancers result from

genetic abnormalities. That's what cancer is.
Q. Is it also true those genetic mutations or abnormalities could be secondary to environmental factors?
A. Yes.
Q. So in that sense, almost all cancers are not only genetic but only environmental in basis?
A. That's incorrect.
Q. Are you aware of individuals who published to the contrary?
A. I'm not sure. I would have to see the actual papers that you are referring to because that's your interpretation. I'm not sure that I would agree with your characterization of the papers.
Q. Do you agree that cigarette smoking is linked to the development of lung cancer?
A. Yes.
Q. Do you agree that excessive UV light is associated with the development of cancer, specifically especially malignant melanomas?
A. Skin cancer in general, yes.
Q. In fact, you have said people who use tanning beds have over a 50 percent increased risk of developing melanomas. Correct?
A. Yes.

Q. That's as a result of the UV light?
A. That's correct.
Q. The UV light is an environmental factor. Right?
A. Absolutely.
Q. Not everyone who sits long-term in tanning beds develop cancer?
A. That's correct.
Q. In fact, only 10% of long-term smokers, those with high pack year histories, develop lung cancer?
A. I believe I put that in my report.
Q. You did. That would indicate there is a genetic component also. Correct?
A. Not exactly correct. Can I elaborate?

Again, this is one of the areas that's very confusing to the lay public. All cancer is genetic in the sense that it derives from changes in genes or their gene expression. By that criteria, that's how scientists talk about cancer. There is not a single credible scientist who would say that cancer is not a genetic or genomic disease. What you are, I believe, referring to are inherited genomic predispositions, or something like that. That's different than saying cancer is not genetic. All cancer is genetic.

Q. There is a difference between inherited mutations and somatic?

A. Yes.
Q. Can you explain to the Court what is meant by a somatic?
A. A somatic mutation is one that occurs after birth.
Q. On page 68 of my outline, looking at your expert report, Doctor, it is your opinion most cancer causing somatic mutations probably occur as a consequence of unrepaired errors in DNA replication and are thus mere bad luck. Put another way, the cancer causing environment is our own body and the enemy lies within. That's your opinion. Correct, sir
A. I wrote it in my report, yes.
Q. You have four references after that?
A. Yes.
Q. All four references by Tomasetti and Vogelstein?
A. Yes.
Q. Now, as you mentioned a moment ago, first of all, it is your opinion 60 percent of cancers are preventable. Correct?
A. Yes.
Q. Not just bad luck?
A. Well, the environment, your body is still causing the cancers, yes.
Q. Now, the publications by Tomasetti and

Vogelstein, that resulted in a impressive controversy in the medical literature, did it not?
A. Yes.
Q. But you provide four articles by just Tomasetti and Vogelstein?
A. Yes.
Q. Now, can you go to Exhibit PSC Neel 21. There is a paper by Tomasetti and Vogelstein titled, "Variation in Cancer Risk Among Tissues Can Be Explained by the Number of Stem Cell Divisions."
A. Yes.
Q. This is part of the literature search you did in finding these articles, sir?
A. Yes.
Q. And you are utilizing these articles as giving a fair and balanced approach to what your opinions are in this litigation?
A. I don't remember if I cited this particular paper. I would have to see.
Q. I believe this is your reference No. 14.
A. Okay.
Q. Now, amongst the responses when this paper was published -- first of all, if you look four lines up from the time they say, "The majority is due to bad luck, that is, random mutations arising during DNA

replication in normal noncancerous stem cells." Correct?

A. Yes.

Q. You put that in your expert report?

A. Yes. Not exactly the same statement.

Q. Now, if we could go to Exhibit PSC Neel 12, there is a paper by Nowak and Waclaw, titled, "Genes Environment and Bad Luck," explain cancer risk in a statistical sense. This was published in Science in March 2017, and Science is a highly rated scientific journal. Correct, sir?

A. Yes.

Q. You are not a statistician. Correct?

A. No.

Q. Now, in the first paragraph of this paper they write:

"It is a human trait to search for explanations for catastrophic events and rule out mere chance or bad luck. When it comes to human cancer, the issue of natural causes versus bad luck was raised by Tomasetti and Vogelstein about two years ago. Their study, which was widely misinterpreted as saying that most cancers are due neither to genetic or inheritance nor environmental factors but simply bad luck, sparked controversy. To date, a few hundred

papers have been written in response including two to six with some such as two coming to opposite conclusions."

Do you agree the Tomasetti/Vogelstein paper sparked controversy?

A. Yes. I'm not claiming all cancers are caused by bad luck. I'm saying definitely -- multiple things contribute to any given cancer. Inherited predisposition can contribute. Abnormal replication errors that just occur by bad luck, and in some cases environmental agents.

Q. In your expert report, which Her Honor read and has to read, you wrote specifically: "Rather most cancer causing somatic mutations" -- somatic being after birth -- "probably occurs as a consequence of unrepaired errors in DNA replication and are thus mere bad luck"?

A. I think the context is that not all cancers are caused by environmental agents; and if I miswrote or misspoke, I'm happy to clarify.

Q. It's not your opinion as an expert in cancer biology that women who have developed ovarian cancer perhaps due to long-term genital use of talc didn't get the cancer from the talc but it is just bad luck on their part. That's not their testimony, is it?

A. That's a very difficult question. It is my testimony that there is no evidence perineal application of talc contributes to ovarian cancer in any woman. That is my testimony. That's more clear.
Q. Looking at those studies that have a contrary opinion the epidemiological studies that come to a contrary opinion, it is not your opinion that talc had no role at all because this is all due to merely bad luck?
A. That's a mischaracterization of my opinion.
Q. If so, I apologize, and I just want that clarified.
A. Would you like me to clarify my opinion? That is a mischaracterization of my opinion.
THE COURT: Tell me what your opinion is.
THE WITNESS: My opinion is there is no evidence from the epidemiological studies alone that makes it more likely than not that perineal talc causes ovarian cancer. That's my opinion.
BY MR. RESTAINO:
Q. Have you seen the epidemiological studies that have found an increased risk between long-term exposure to talc and ovarian cancer?
A. Yes, I have.
Q. That is evidence in and of itself. Correct?

A. No. That is evidence of an association between a particular agent and a particular outcome. There are also many other studies that show the opposite including the more compelling studies.
Q. Compelling in your opinion?
A. Compelling as I understand it from all epidemiologists that cohort studies are more reliable than case-control studies. As I said, I'm not an epidemiologist.
Q. Would you agree a properly designed, properly performed case-control study outweighs a poorly designed, poorly conducted cohort study?
A. I don't have an opinion on that.
Q. You agree smoking causes cancer?
A. Smoking causes several kinds of cancer, yes.
Q. You would agree asbestos causes lung cancer?
A. Yes.
Q. Do you know if there is an actual increased risk in individuals who both smoke and are exposed to asbestos?
A. Yes.
Q. That would be known as the -- could be described as dramatically cocarcinogenic. Does that sound familiar?
A. Yes. I think I wrote that.

Q. Are you familiar with the epidemiological term "interaction or effect modification"?
A. I'm not an expert in epidemiology. I've read that. I can't state with confidence what that means.
Q. How about if we just go along with "dramatically cocarcinogenic," inasmuch as you wrote that?
A. I understand what that means.
Q. There are risk factors associated with the development of ovarian cancer. Correct?
A. Yes.
Q. If we can turn to your expert report, page 12. In the bottom paragraph you have a section that you wrote, expert report.

Sir, you wrote:

"Multiple factors rather than a single cause likely contribute to ovarian cancer generation. It is difficult to attribute a specific case of cancer to a single cause."

You wrote that, sir. Correct?

A. Yes.
Q. In fact, it is true that most disease states are multifactorial with the exception of trauma or direct poisoning. Don't you agree?
A. I think that's generally true, yes.
Q. Most causes are multifactorial. Would you

agree?
A. I don't know what you mean.
Q. In order to determine something is actually caused in effect most of the time, that's multifactorial?
A. I'm not sure I thought that through enough to give a yes or no answer.
Q. If we go to page 13 of your expert report, you are discussing risk factors, you write:
"There are several clearly established risk factors for all ovarian cancer and others for specific types" reviewed in 43.
A. Yes. Can I clarify?
Q. Of course.
A. (Continued reading.)
For example, those risk factors were attributed to all ovarian cancers. It doesn't mean that the studies actually broke out their attribution to specific subtypes, and I think I was a little loose in the way I wrote that sentence.
Q. Take a look at that. Your reference is reference 43, "Reid, et al, Epidemiology of Ovarian Cancer, a Review."
Sound familiar, sir?
A. Yes.

Q. Now --
A. That's by Tom Sellers, the senior author on that paper.
Q. If you go --
A. Can you tell me what exhibit that is?
Q. PSC Neel 16.
A. What page?
Q. Page 11. There is a section there titled "Genetic Epidemiology."
See that?
A. Yes.
Q. Reference 43, they write:
"One of the most significant risk factors for ovarian cancer is a family history of the disease. First degree relatives of probands have a 3 to 7 fold of increased risk especially if multiple relatives are affected and at an early age of onset."
Did I read that correctly?
A. Yes.
Q. A proband is the starting point in a family for a genetic study?
A. It is the person in this case who has the cancer. Probably, that's what they meant.
Q. Doctor, you would agree it is biologically plausible for a family history of ovarian cancer to be

a risk factor for the development of ovarian cancer?
A. This is one of those cases where I feel I wasn't exactly accurate. Some of the genetic predispositions that Dr. Sellers cites in his paper are only risk factors for one subtype of ovarian cancer. For example, BRCA1, BRCA2, those DNA repair mutations are all high grade serous cancer risk factors.

However, this paper by Reid does not break down the description of ovarian cancer and risk factors to subtypes, does it?
A. At this time, actually does, if you read the paper.
Q. Let's go through the different risk factors and their references. Reid provides four references for the statement, "The risk of ovarian cancer and first introduce degree relatives are probands, 43 to 47."
A. Okay.
Q. Did you pull those references numbers 43 and 47 to review them?
A. I would have to go see 43 and 47.

No, I didn't read those papers. It's well known those genes cause high grade serous ovarian cancer. The mutations in those genes are risk factors for high grade serous cancers.
Q. The four references that Sellers -- that they

referenced, these are four epidemiological studies published in the peer-reviewed literature. Correct?
A. I didn't read them. I assume they are epidemiological studies.
Q. Because you are relying on what Dr. Reid wrote as your reference?
A. I'm relying on the fact BRCA1 and BRCA2 and these genetic factors are associated with high grade serous ovarian cancer. That is well-established knowledge for anybody who works in the field of ovarian cancer.
Q. You referenced Reid for your statement there are several clearly established risk factors for all ovarian cancers. Right?
A. I did write that. I meant that some papers will say ovarian cancer and not break it down; especially the earlier papers which were published before these subtypes were appreciated.
Q. In the same exhibit, if we go to page 11, on the right column there is a heading risk factors and preventive factors, hormonal and reproductive risk factors. See that?
A. Yes.
Q. They write there:
"Epidemiological research has clearly

implicated hormonal and reproductive factors in the pathogenesis of ovarian cancer."

Do you agree epidemiological research has clearly implicated hormonal and reproductive factors in the pathogenesis of ovarian cancer?

A. Yes. But with qualifications that, for example, the risk for hormonal factors appear to be more for the Type I endometrioid tumors, for example.

Q. Is it biologically plausible for a woman without a history of giving birth to have higher risk factors for the development of ovarian cancer?

A. Yes, it is biologically plausible.

Q. They next describe age at menarche and age at menopause. They write:

"According to incessant ovulation hypothesis, early age at menarche and late age at menopause increases risk by increasing the number of ovulatory cycles."

Did I read that correctly?

A. Yes.

Q. Do you agree that the incessant ovulation hypothesis, at an early age of menarche and menopause at a later age increase the risk of ovarian cancer?

A. With the qualification Dr. Sellers also makes on page 13 at the end of the paragraph, regardless the

available --

THE COURT: Slow down a little bit.

A. Sorry. On page 13 Dr. Sellers also writes:

"Regardless, available evidence suggests the magnitude of any effect is small."

With that qualification, which Dr. Sellers has also made in his review,.

Q. "Small" still means there is an increased risk?

A. There is an increased risk, yes.

Q. And it is an huge increased risk for the woman who develops ovarian cancer?

A. That's hard to answer. You can't make a risk assessment for an individual.

THE COURT: He didn't expect an answer to that. It is more of a statement.

THE WITNESS: I'm trying to help.

Q. Dr. Reid also provided references for the notion that the increased risk of ovarian cancer associated with the age of menarche and menopause. Did you pull those studies and review them.

A. I probably looked at some of them but not all of them. Again, the purpose of my report was to assess the biological experiments. I read the epidemiological experiments to see if there was any evidence at all in favor of the hypothesis.

Q. Doctor, parity indicates a number of pregnancies reaching viable gestational age, including live births and still births. Correct?
A. Yes.
Q. They have a section on page 13 they titled "Parity and Infertility." See that?
A. Yes.
Q. They write:
"The association between pregnancy and ovarian cancer risk has been studied extensively."
See that, sir?
A. I do.
Q. Do you agree that association has been studied extensively?
A. I think Dr. Sellers would be more able to make that statement than I, but yes, I agree.
Q. Further down they write:
"Indeed, parous women have a 30 percent to 60 percent lower risk than nulliparous women" and they have many references, "and each additional full-term pregnancy lowers risk by approximately 15 percent. Did you pull all those references?
A. I did not pull all of those studies, no.
Q. Do you know if any of those referenced epidemiological studies break down the analysis by

ovarian cancer subtype?

A. I don't know if those studies do that, but a more recent study does.

Q. Is that more recent study published in your expert report?

A. It is in my supplemental report. It is not in my original report.

Q. Now, continuing on, on page 13 they have a section on lactation. Do you see that, sir?

A. Yes.

Q. Once again they write:

"Both the incessant ovulation and gonadotropin hypotheses would predict lactation reduces the risk of ovarian cancer. In fact, most studies indicate a slight protective affect from breast feeding with odds ratio approximating 0.6, to 0.7" with many references "although some have not,." And other references.

Correct?

A. Yes.

Q. Did you pull those epidemiological studies?

A. No.

Q. Do you know if any of those studies in this paper by Reid et al, which is your reference 43 and you are relying upon break down the ovarian cancer by subtype?

A. I don't.
Q. If we go over to page 14, right column, final paragraph:
"Several gynecologic procedures appear to influence the risk for ovarian cancer. It is well established that among high risk women bilateral prophylactic oophorectomy decreases risk by at least 90 percent reference 176."
Do you agree with Reid at all that several gynecologic procedures appear to influence the risk of ovarian cancer?
A. Yes.
Q. Do you agree it is well-established among high risk women bilateral prophylactic oophorectomy decreases that risk by at least 90 percent?
A. Yes.
Q. Did you pull that reference?
A. I don't recall if I pulled that reference. That's well-established.
Q. And that looks at ovarian cancer in general, not by subtype. Correct?
A. Yes.
Q. Now, Doctor, is it biologically plausible for a woman who has undergone a tubal ligation -- for a woman who has not undergone tubal ligation to be a

risk factor for ovarian cancer -- how about if I strike that and try that in English.

Is it biologically plausible for a woman who has not undergone a tubal ligation to have a higher risk for the development of ovarian cancer?

A. Actually, if you read the complete context of Dr. Sellers' review, you will notice in the last sentence of that section, says:

"Indeed, this hypothesis is supported by epidemiological studies that show the strongest associations between tubal ligation and ENOC carcinoma and CCOC" -- which stands for clear cell carcinoma.

A. Again, there is biological plausibility for that because it blocks the egress of endometriotic lesions from the uterus to the tube. I think that's a good example of how modern epidemiology would in fact break ovarian cancer into separate diseases, as I said in my expert report and I said this morning.

Q. Now, you referenced the Reid and Sellers paper?

A. I did.

Q. To support your opinion regarding risk factors for ovarian cancer?

A. Yes.

Q. In this paper not only their opinions regarding risk factors but all the supporting epidemiological

studies there all look at risk factors as it relates to the development of ovarian cancer, and you did not state that this paper should be read with skepticism, did you?

A. I said -- I did not state this paper should be read with skepticism, no.

Q. But you did write studies including epidemiological reports that treat ovarian cancer as a single entity should in your opinion be viewed with skepticism?

A. Yes. Both statements are correct.

Q. Now, there is a couple of other risk factors that Reid and Sellers did not discuss, and that would include, for example, Jewish ethnicity. Correct?

A. They did not discuss it.

Q. But it is biologically plausible for some woman of Jewish ethnicity to get ovarian cancer?

A. If they have a BRCA mutation.

Q. And Reid et al did not discuss long-term genital talc use as a risk factor for ovarian cancer?

A. They actually did discuss long term genital talc use for ovarian cancer. It is on page 18. Can I read it?

Q. Sure.

A. (Reading.)

"Mechanistic pathology in animal studies do not support:

THE COURT: That's clearly not slow.

A. This is on page 18.

"While mechanistic, pathology, and animal studies do not support evidence for the carcinogenicity of talc on the ovarian epithelium epidemiological studies have indicated an association of talc use in increased ovarian cancer risk."

I agree with that. I agree completely with Dr. Sellers' opinion. There is no animal, mechanistic, pathological, or other evidence for an effect of talc on the ovarium epithelium, and I would add the Fallopian tube epithelium to that.

Q. But there is epidemiological evidence?

A. There is some epidemiological evidence which she discusses in this review, and I'm sure I read all of those papers which was the subject of my expert report.

Q. Now, when you were doing your initial PubMed search and utilizing key words such as "ovarian cancer," did you find a paper titled, "Opportunities and Challenges in Ovarian Cancer Research, a Perspective from the 11th Ovarian Cancer Action/HHMT Forum, Lake Como, March 2007"?

A. I don't believe I read that.
Q. Have you ever seen this paper?
A. No. I'm just seeing it now. That's like ancient history 2007.
Q. The Bible is from ancient history --
THE COURT: That's not appropriate. Let's move on. We are talking science today.
Q. This was published in Gynecologic Oncology in 2008. Correct?
A. Yes.
Q. Not referenced in your expert report?
A. No.
Q. Not listed in your reliance list?
A. No.
Q. Not listed in your supplementary reliance list?
A. No.
Q. Has "ovarian cancer" in the title?
A. Yes, it does.
Q. If you go to the tab which is PSC Neel 24, they write: "Identification of woman at increased risk will facilitate prevention and early detection in subsets of patients." As a physician, you would agree that's a good thing to do. Correct?
A. Absolutely.
Q. Now, if you go on to the first page, the right

column, at the bottom of the first paragraph, this is PSC Neel 24:

"Aside from genetic profiling there may be reproductive or environmental risk factors which could be combined to identify women at increased risk for the disease. Such women might be candidates for more intensive screening or chemo or immune prevention."

Did I read that correctly?

A. Yes.

Q. We just went through with the Reid and Sellers paper reproductive and environmental risk factors, did we not?

A. Yes.

Q. Which could be combined to identify women at increased risk that's akin to smoking and asbestos, and I think your co-carcinogenic risk factors combining smoking, combining asbestos, you get a higher risk than each agent by itself.

Do you understand that, sir?

A. Sure. Absolutely. Yes. Although it is not the case all risk factors when combined would increase the ability to prevent things. There could be antagonistic effects, but just to be clear.

Q. That could be adjusted for in any epidemiological studies?

A. Epidemiological studies are basically attempts to do that. You have to do a prospective study to see whether it is successful.
Q. To see what is successful?
A. Epidemiological studies can suggest a strategy, but you have to do a prospective study to see whether it actually works.
Q. You are saying that as an expert in epidemiology?
A. As an expert in medicine.
Q. If I conducted a study retrospectively looking at miners from the state of Colorado that both smoke and are exposed to radon and look at their medical history and I determine that smokers have an odds ratio of 25 where as those exposed to radon have a risk factor of four, and when combining them to affect modification see a risk of 100, is that an invalid study?
A. No. That's such a strong risk factor that it makes a big difference. I misspoke.
Q. Let's go to the next paragraph which starts:
"A combination of demographic reproductive and environmental risk factors might be used to develop a model that would more accurately predict risk. One preliminary algorithm using seven risk factors -- in

parenthesis age over 45, long-term genital talc use, family history of ovarian cancer, early onset breast cancer, Jewish ethnicity, no oral contraceptive OC use, no live birth, no breast feeding, no tubal ligation, show that women with six to seven of these events have an odds ratio of 7.55."

Did I read that correctly?

A. Yes.

Q. Now, those risk factors that are listed there. We just went through many with the exception of Jewish ethnicity described in your reference 43, the Reid/Sellers paper. Correct?

A. Yes.

Q. Now, OR equates to an odds ratio. Correct?

A. Yes.

Q. An odds ratio of 7.59 equates to an increased risk of 659 percent. Correct?

A. I would have to do the calculation but I would trust you.

Q. An odds ratio of 1 means no increased risk?

A. Yes.

Q. It's the background rate?

A. Yes.

Q. If we go up to 0 1.5 we have a 50 percent increased risk.

A. Yes. I'm not contesting your math.
Q. Now, the co-authors of this paper -- the conference was in 2007, the paper was published in 2008 -- reported on this algorithm indicating that a woman with six to seven of these events, including long-term genital talc use, had an increase of 659 percent of developing ovarian cancer, and you didn't find this study, sir?
A. I remember seeing the study on that model. I do remember seeing that study, but I don't remember in detail what it said.
Q. Now, if we go down further in the paper we see a list of authors.
A. Yes. I have the list.
Q. Now, at the second author is Frances Balkwill. Frances. You know Dr. Balkwill?
A. Yes.
Q. You recognize her as an esteemed researcher in the area of ovarian cancer?
A. Along with Dr. Boyd who is also listed as an expert.
Q. That would be Jeffrey A. Boyd, who is a defense expert?
A. Yes. Actually, I recognize most of them.
Q. In fact, you had Dr. Balkwill as one of your

lead speakers at the AACR meeting in 2012 that you chaired. Correct?

A. Correct.

MR. RESTAINO: Your Honor, would this be a good time to take a lunch break?

THE COURT: Yes.

THE DEPUTY CLERK: All rise.

(The luncheon recess is taken.)

(Continued on the next page.)

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A F T E R N O O N S E S S I O N

THE DEPUTY CLERK: All rise.

THE COURT: Thank you.

BENJAMIN G. NEEL, resumed

CROSS-EXAMINATION (continued)

BY MR. RESTAINO:

Q. Good afternoon, Dr. Neel.

A. Good afternoon.

Q. Dr. Neel,, I'm just going to finish off where we left, the studies regarding risk factors and the Lake Como studies, and I would like to put up on the screen your deposition testimony.

You were asked --

MS. SHARKO: I object. This isn't proper use of the deposition. There is no contradiction.

MR. RESTAINO: I think it is complete contradiction.

MS. SHARKO: I don't think it is proper use of deposition testimony.

THE COURT: Take it off. Ask him the question and see if he agrees with that. It will still happen, I'm sure.

BY MR. RESTAINO:

Q. Dr. Neel, can credible scientists look at the evidence and determine the genital use of talcum powder is a risk factor for ovarian cancer?

A. Not in 2019, no.

Q. That's because of the epidemiological studies that have been published since then?

A. No, the biology studies that show no evidence of causation.

Q. And you are relying strictly on biology studies for that?

A. Those are the primary studies I reviewed as part of my expert report.

Q. If there is a biology study that has an unknown mechanism, you would not agree that study could indicate carcinogenicity in a human being. Is that true?

A. That's a hypothetical. I don't know what you mean by a biological study without a mechanism.

Q. A molecular mechanism study.

A. I don't think there is any biologic evidence talc causes ovarian cancer. Is that fair?

Q. Did you write your expert report with the same care that you used in writing your published papers?

A. I tried to.

Q. You recognize there are some errors in your expert report or misquotes as you used them so far this morning? Have you had papers returned by reviewers indicating that changes needed to be made?
A. Absolutely.
Q. In fact, it is not uncommon to send in a published or a manuscript for publication to one journal and have the journal, for whatever reason, reject it and have it published in another journal. Correct?
A. That's correct.
Q. That happens all the time actually?
A. Yes.
Q. Now, let's turn to your expert report. I'm on page 53 of the outline -- your expert report on page 17, I believe, and it is paragraph B. You start off with a quote, "MPO"?
A. Yes.
Q. "MPO and iNOS are highly expressed and co-localized in EOC cells"?
A. That's referring to a quote from Dr. Saed's paper.
Q. It is indeed. It is from Dr. Saed's report, the bottom of page 5. And you write:
"Even if this statement were true," this

statement may in fact be true.

Correct?

A. I don't agree that it's true; but even if it were true it's a non sequitur. That's what I wrote.

Q. The statement may be true?

A. No, that's not what I'm saying.

Q. You write, "Even if the statement were true" --

A. That's a hypothetical, if it were true, it's a non sequitur. If you read the rest of it, you will see it isn't.

Q. Let's go to Dr. Saed's report, the bottom of page 5.

THE COURT: Is page 5 quoting from his expert report or his manuscript?

MR. RESTAINO: The expert report.

Q. (Reading.)

"My laboratory has previously reported that MPO, a hemoprotein present solely in myeloid cells that acts as a powerful oxidant, and iNOS, a key pro-oxidant enzyme, are highly expressed and co-localized to the same cell in EOC cells."

A. I don't have his report, but I believe that's what he wrote, yes.

Q. He has a reference there. Correct?

A. Yes.

Q. Reference 17, which is the paper published 2010 in Gynecologic Oncology?
A. Yes.
Q. A well-respected journal?
A. Yes.
Q. Now, you find this seriously flawed?
A. Yes.
Q. The peer reviewers did not?
A. They made a mistake, and there is knowledge since that time that helps to address that mistake.
Q. The editor did not have a problem with this and it was published. Correct?
A. Yes. There are many things published that are not accurate.
Q. If this was seriously flawed, since this time in 2010, did you see a single letter to the editor of the journal Gynecological Oncology pointing out serious flaws in Dr. Saed's manuscript?
A. No.
Q. Did you write a letter to the editor at the time indicating this paper had serious flaws?
A. I didn't read the paper at the time.
Q. You only read this paper after you were retained as an expert by Johnson & Johnson. Correct?
A. This particular paper, that's correct.

Q. Are you planning on writing a letter to the editor of the journal indicating this study has serious flaws?
A. I hadn't thought about it.
Q. MPO is an oxidant and an inflammatory marker?
A. It is a pro-oxidant molecule inside of myeloid cells, but it is not a marker of inflammation.
Q. Has it been shown in ovarian cancer to affect proliferation and apoptosis?
A. Dr. Saed I believe claimed that, but it is not expressed in ovarian cancer cells.
Q. Now, is your opinion that any effect on any cell line by talcum powder is irrelevant?
A. No. It depends what the question is. Irrelevant to what?
Q. Irrelevant to biological activity.
A. It depends on the context.
Q. Is it relevant to biological activity resulting in inflammation?
A. Not if it concerns the ovarian cancer cell, no.
Q. Regarding the criticism of the SKOV-3 cell line, in the same paragraph SKOV-3 is in fact still the most widely used cell line for ovarian cancer. Correct?
A. I don't know if it is still. It depends on the context.

Q. Have you seen any recent publications -- and I'll limit it to 2018, 2019 -- advising the general scientific community to not use SKOV-3 as a cell line for study of ovarian cancer?
A. There are three papers published, but not in 2018, that did make exactly that advice.
Q. There are also papers that follow that in response indicating the value of SKOV-3 for studying ovarian cancer. Right?
A. I don't know which papers you are referring to.
Q. You didn't review both sides of those?
A. It is not two sides to that. It is well-established from the genetic data that SKOV-3 is not a serous ovarian cancer line. That is what the controversy is about.
Q. What there is no controversy about, it is generally accepted to test in that cell line for an effect for ovarian cancer and then, if necessary, check another cell line?
A. No, that's incorrect in my opinion.
Q. In your opinion?
A. Yes.
Q. Now, in paragraph C of your expert report on page 18 you wrote:
"Common SNPs in the redox enzymes are known to

be strongly associated with altered enzymatic activity that has been linked to ovarian cancer," and you put pages 7 and 8, quoting Dr. Saed. Correct?

A. Correct.

Q. In fact, Dr. Saed does not state altered enzymatic activity has been linked to ovarian cancer; does he?

A. I don't have his expert report so I can't comment on that.

Q. Let's turn to his expert report. And the section entitled, "Common Polymechanism and Reduction Enzymes Are Associated With Ovarian Cancer." What he actually writes is:

"Common SNPs in the redox enzymes are known to be strongly associated with an altered enzymatic activity in these enzymes and helps explain the enhanced redox state that has been linked to several malignancies including ovarian cancers."

Correct?

A. That's what he wrote, yes.

Q. This has been generally accepted by the scientific community?

A. No, it has not.

Q. Dr. Saed provide two references for this statement which are not in your expert report?

A. I don't have the references in front of me, so I can't comment on those references. If you want to give me his expert report, I would be happy to help.

THE COURT: We can get it from chambers.

MS. O'DELL: Judge, that would be helpful.

(Pause.)

THE COURT: You are checking the cites 12 and 16.

THE WITNESS: Reference 12 is Dr. Saed's own paper and reference 16 is a paper about -- I haven't read that paper but that's not relevant to the question whether these SNPs are linked to a redox state. I don't believe this paper has anything to do with those SNPs. In any event, those SNPs are not associated with ovarian cancer which is what I was writing.

BY MR. RESTAINO:

Q. Doctor, you didn't read this. The first one is published in Reproductive Sciences and the second one is published in Gynecologic Oncology, two peer-reviewed journals. They have been peer-reviewed and published. Right?

A. As I recall, I think you asked me if it has been validated by others. The first paper is Dr. Saed's paper. That's not "others." The second paper, I

don't remember if I read it or not, but I don't believe that has anything to do with the SNPs. And I checked for the SNPs, which is what I was writing about in that paragraph.

Q. Doctor, there is nothing wrong with quoting one's previous work from a laboratory, and that happens all the time?

A. Absolutely. I wasn't questioning that. You said by others and I was answering that.

Q. Once it is published, are there any letters to the editor in any of these journals pointing out flaws or errors in these papers?

A. Not to my knowledge.

Q. Paragraph E on page 20 of Dr. Saed's expert report -- I'm sorry -- of your expert report.

A. Yes, I see it.

Q. You wrote: "Talc initiates an inflammatory response." Page 10-11. Is that correct?

A. Yes.

Q. Now, if you actually go to Dr. Saed's report from that section, he writes:

"Asbestos fibers in the lung initiate an inflammatory and scarring process, and it has been proposed that ground talc as a foreign body initiates a similar inflammatory response, and it has been

proposed that ground talc as a foreign body might initiate an inflammatory response."

Isn't that correct?

A. That's what he writes, yes.

Q. That's fundamentally different than what you wrote as a synopsis of saying talc initiates an inflammatory response. Correct?

A. I don't think so, no.

Q. As you wrote it, and in your experience as a peer reviewer and editor, this would not be accepted for publication in a peer-reviewed journal, the way you mischaracterize that full sentence by Dr. Saed?

A. I don't think this mischaracterizes the sentence insofar as it appears to talc. If you believe it was a mischaracterization, I apologize. That's not what my intent was, to mischaracterize his statement.

Q. Now, if we go to paragraph G of your report, page 21, you write:

"Migration/transport of particles through the genital tract is universally accepted."

Correct?

A. Yes.

MR. RESTAINO: I'm going to withdraw the question. I didn't strike that out.

Q. If you go to your expert report, page 23,

paragraph K, in the middle of the paragraph you write:

"He does not seem to be aware of recent evidence that full blown cancers are often more sensitive to oxidative stress. Reference 12. Indeed, one therapeutic approach under investigation in several laboratories is to promote increased oxidative stress in cancer cells."

Did I read that correctly?

A. Yes, you did.

Q. Now, reference 12 is the two phases of reactive oxygen species in cancer?

A. Yes.

Q. They write there:

"Reactive oxygen species is not appreciated for their cellular signalling capabilities for having a dual role in cancer."

Isn't that true?

A. I don't remember the paper by heart. Can you please tell me where to find it and we can discuss it.

Q. Let me ask you --

A. I'll agree with that statement.

Q. You would agree with it?

A. Yes.

Q. And yet on the one hand ROS can promote protumorigenic signalling. Correct?

A. In certain cells, yes.
Q. That would facilitate cell proliferation?
A. That's a little more complicated than that. I don't think that's exactly an accurate statement as you've made it. Definitely in certain contexts, oxidative stress can contribute to cancer.
Q. Do you agree that ROS can promote and facilitate cancer cell proliferation?
A. Not directly. Indirectly.
Q. Resulting in cellular proliferation?
A. All cancer cells proliferate. You are oversimplifying a complex issue with respect.
Q. Do you remember in your expert report, from what I'm reading, you have a reference 12. Correct?
A. Yes.
Q. Do you know what reference 12 is?
A. Not by heart. I'll have to look it up.
Yes, I know the paper and know the author.
Q. They state therein that ROS can promote cellular survival also. Correct?
A. Indirectly by causing mutations.
Q. And adaptation to hypoxia?
A. Yes.
Q. On the other hand, ROS can promote anti tumor genetic signalling and trigger oxidative-induced

cancer cell death?
A. Yes. That's what I was referring to in that sentence.
Q. When you indicate Dr. Saed does not seem to be aware of recent evidence that full-blown cancers are often more sensitive to oxidative-stress, citing this paper, this paper does indicate there are the two sides of the coin.
A. Yes. I'm aware of both sides.
Q. And Dr. Saed is pointing out one side of that coin?
A. Yes. But he's not pointing out the other side. He was implying, I believe, in the context I was writing that he was implying oxidative stress is always good for cancer cells.
Q. Is that what Dr. Saed's manuscript states?
A. Yes. In my opinion, yes.
Q. In your opinion?
A. Yes.
Q. Now, if we could turn to your expert report, page 22.
A. Yes.
Q. You write:
"Similarly, Reviewer Two noted that, quote, their data do not show, despite the author's claim,

any evidence that these cells are transformed, i.e. malignant... Consequently, neither tumor initiation nor progression is documented in this study as opposed to the statement in highlight No. 1 in the text and elsewhere."

Did I read that correctly?

A. Yes.

Q. Now, if we put up what Reviewer Two actually stated, you see they write:

"Their data do not show, despite the author's claim, any evidence that these cells are transformed" -- however you leave out -- "specifically, no experiments documenting changes in cell survival, proliferation, or resistance to apoptosis have been performed." Correct?

A. Yes.

Q. And you didn't include that sentence in your expert report. Correct?

A. I don't think it changes the context of my statement.

Q. Would it change the context of your statement if in fact those studies were in fact performed?

A. No, because the last statement is still true.

Q. Do you know if in the published final manuscript by Fletcher and Saed, if in fact they documented

increased cell proliferation and decreased apoptosis as this Reviewer No. 2 recommended.

(Pause.)

A. Yes. In the finally published manuscript are experiments that purport to examine those questions but both of the experiments are seriously flawed in my opinion.

Q. Have you written a letter to the editor pointing out that those observations are flawed in your opinion?

A. No.

Q. Has anyone written to the journal?

A. Not that I know of.

Q. Doctor, Dr. Saed never said that CA-125 indicated the pathogenesis of ovarian cancer, did he?

A. He said it was a hallmark of ovarian cancer. That may be a misstatement or may be a misunderstanding on my part what he misrepresents by hallmark.

Q. Do you consider CA-125 to be the gold standard tumor marker in ovarian cancer?

A. For monitoring the amount of tumor, yes.

Q. And do you agree the pathogenesis and development of ovarian cancer have been closely linked to inflammatory process?

A. Could you repeat the question a little bit slower. I'm not sure I followed that.
Q. Would you agree the pathogenesis and development of ovarian cancer have been closely linked to an inflammatory process?
A. If by pathogenesis and development you mean once the cancer is established that it is linked to inflammation, I think that is an accurate statement. If you mean inflammation has been shown to induce or initiate ovarian cancer, I think that remains in the realm of hypothesis or speculation.
(Pause.)
Q. Doctor, are you familiar with the study, the Balkwill and Mantovani article?
A. Yes, it is a review article.
Q. Titled, "Inflammation and Cancer Back to Virchow."
A. Yes. I am familiar with the paper.
Q. And you are familiar with Dr. Balkwill and Dr. Mantovani.
This is published in the Langseth?
A. In 2001.
Q. Now, if you turn to panel one of the document.
A. What exhibit is that, please?
Q. Seven. Panel 1 now. It should be on here.

MR. RESTAINO: We'll move on. I'll strike it.

Q. Doctor, are you familiar with the National Cancer Institute?

A. Yes.

Q. Does the National Cancer Institute, to the best of your knowledge, associate asbestos with the formation of malignant mesothelioma, pleural peritoneal, and ovarian cancer?

A. I believe that's in the PDQ link for ovarian cancer.

Q. Now, if we have PSC 19, and this is a review article. The author is Sekido out of the Division of Molecular Oncology in Japan; again, a review article as we discussed, typically written by someone learned in the area. Correct?

A. It depends on the journal in which it is published.

Q. Now, if we move down to page 1, the right column, second full paragraph, they have a section there, "Genetic Damages Induced By Asbestos."

A. I got it.

Q. See the second paragraph they write:

"After long and thin asbestos fibers are inhaled deeply into the lung and penetrate the pleural space, interaction of asbestos fibers with

mesothelioma cells and inflammatory cells are thought to initiate prolonged cycles of tissue damage, repair and local inflammation which finally lead to carcinogenesis of MM," which they describe as malignant mesothelioma "with unknown mechanisms."

Did I read that correctly?

A. Yes.

Q. To the best of your knowledge, is there a known mechanism by which asbestos fibers today cause the cancers of the pleural space?

A. I'm not an expert in mesothelioma, and I can't comment in an intelligent way on that question at all.

Q. When you went through the Bradford Hill view points, one of the viewpoints is analogy. Correct?

A. Yes.

Q. You would agree analogy to other conditions could be important for an investigator?

A. It would be one of the factors one would weigh in coming to a conclusion.

Q. For example, in today's day and age, it would be incumbent upon a company who is coming up with a new medication to treat morning sickness in women to be aware of what happened with thalidomide?

MS. SHARKO: Objection. This is well beyond the scope of what we are here for, the obligation of a

company to do something.

THE COURT: I think phrasing in the context of the company is not appropriate in your question.

Go ahead.

Q. In today's day and age --

THE COURT: Put it in that context, thank you.

BY MR. RESTAINO:

Q. Thalidomide is associated with phocomelia, or something like that.

In this case we have a known substance recognized by NCI causing cancer in the lung pleural cavity, peritoneal and in the ovary inducing inflammation, but the exact mechanism is unknown.

Doctor, does that mechanism have to be known for one to assume and recognize that asbestos causes ovarian cancer?

A. First of all, I didn't make any statement as to whether asbestos causes ovarian cancer.

Second of all, I did not make any statement as to whether there has to be an expert on mesothelioma, so I can't comment on that on an intelligent way.

Q. Doctor, you didn't provide testimony on your knowledge of any of the constituents that are found and reported to be found in talc. Correct?

A. I'm not sure I understand your question. Maybe

I can answer it in a way that will be clear. What I said was I wasn't aware of any information about the constituents.

Q. And have you undertaken any research since the time of your deposition to determine what constituents are found within talc powders?

A. No.

Q. Do you know if asbestos is present?

A. No, I don't know one way or the other.

Q. Do you know if any form of asbestos is present?

A. I don't know one way or the other.

Q. Do you know if fragrances are present?

A. I don't know one way or the other.

Q. Do you know if heavy metal is present?

A. I don't know one way or the other.

Q. Isn't it important that you are going to be evaluating the potential carcinogenic effect of a substance that you know whether or not a known carcinogen is within that substance?

A. No, not in my opinion, no.

Q. So if someone came to you as the director of your Cancer Institute and asked you to conduct a study looking at the carcinogenic effect of their paint, wouldn't one of the seminal questions be: Well, is there lead in your paint? Because if so there is an

increased risk of liver and esophageal cancer?
A. No. That would not be relevant if I were actually going to do a study to test the substance. That's what biological plausibility means.
Q. Without the presence of lead, it is true, is it not, you keep getting negative results? Because the known carcinogen is absent?
A. I don't know -- you asked me if I was going to test something. I told you how I was going to test. Can you clarify.
Q. If you wanted to establish a study that showed no evidence of carcinogenicity for a particular form of paint, one could say: I want just lead-free paint; and, lo and behold, look, there is no cancer here. Correct?
A. That's incorrect on multiple levels in my opinion.

First of all, I wouldn't design a study to show something. I would design a study to test something. You said if somebody came to me with a substance and asked me to test it, would I know what's in it. The only reason I would need to know what's in it is if I thought it was potentially dangerous to the people who are going to be doing the experiments. But I wouldn't need to know what's in it to do the

experiment and get the result.
Q. So if you did this experiment with paint not knowing if there is any lead in it, and the experiment was negative, then you would say there is no carcinogenic effect associated with this substance. Would that be a valid study?
A. It would be a valid study for the question you asked me to address, which is: Is this substance carcinogenic? And that's what I would do, yes.
Q. Now, if you tested it and it had lead in it, and it had a different effect, wouldn't that be important for you to know?
A. If I tested it, I would know it. I don't understand the question.
Q. If you tested the substance that had lead in it, and you saw a carcinogenic effect, you would come to the conclusion there is carcinogenicity going on here. Correct?
A. Yes.
Q. If you tested a substance with no lead in it, you would say there is no carcinogenicity study. Correct?
A. That would be the correct study. There would be no carcinogenicity to that substance.
Q. Now if you were given an unknown substance and

you don't know it has lead in it, and it comes out with no carcinogenic effect, how could you say there is no carcinogenic effects without knowing there is potentially the presence of a carcinogen in it?

A. With respect Mr. Restaino, you can't prove a negative. You can only test a hypothesis. Beyond your question. That's not the scientific method. The scientific method is pose a hypothesis, design an experiment, do the experiment and decide what the experiment shows you. That's the scientific method.

Q. And in that method, one must adjust potential and known confounders. Correct?

A. Confounders is not a term of biology. Confounders is a term of epidemiology. If you are asking me about biology, I don't know what you mean by "confounders." You have to control for all of the issues in that experiment. And in this experiment, the hypothetical experiment you have outlined to me, you would take a substance, you would test it in the right assay with proper replicate and proper controls, and then you would make proper measurements again with validated assays, and you would come to a conclusion. That is the scientific method -- at least a scientific method of a cancer biologist. And I'm a cancer biologist, so I can give you my opinion on that. I

hope that's helpful.
Q. We'll move on.
You said you reviewed a study by Dr. Shih. Correct?
A. Yes.
Q. That study by Dr. Shih has not been published?
A. That's correct.
Q. That study by Dr. Shih is not complete. Correct?
A. I don't know that this not complete. I have no information one way or the other.
Q. Did you review his deposition?
A. I don't think I read his deposition actually.
Q. Did you discuss his deposition with anyone?
A. No. I wouldn't discuss it with anybody if I hadn't read it. It would be hard to discuss.
Q. And Dr. Shih obtained histopathology slides from a grant, and the slides include evidence of ovarian cancer, normal ovarian tissue, Fallopian tissue. Correct?
A. Yes.
Q. And Dr. Shih looked in the slides and observed those slides that had evidence of STICs. Correct?
A. Yes, and p53 signatures to be complete. It also had p53 signatures in that, yes. There were several

samples that had p53 signatures.
Q. And he looked for evidence of inflammation?
A. Yes.
Q. And he looked for inflammation as evidenced by the presence or absence of lymphocytes. Correct?
A. It was the presence and absence of macrophages, neutrophils and lymphocytes.
Q. Did he list presence of macrophages and neutrophils in his report?
A. I don't recall, to be honest. That was my recollection, but I haven't read that in a while, maybe a week.
Q. Because macrophages as we discussed are another marker of inflammation?
A. Macrophages are normal cell types, so they are not by themselves a marker of inflammation. Excessive macrophages in full penetration into tissues would be a marker of inflammation.
Q. Lymphocytes are a marker of inflammation?
A. Again, to be clear, lymphocytes are normal cells in the body, and excessive accumulation of lymphocytes could be a marker of inflammation. It's the excess that's the critical point.
Q. In fact, that's what Dr. Shih was looking for, the evidence of inflammation. Correct?

A. Correct.
Q. His hypothesis was that if the STICs are developing as a result of inflammation, there must be inflammation around them. Correct?
A. I believe that was his hypothesis, yes.
Q. But if he did not see an increased number of lymphocytes and did not report whether there were macrophages or any other cells associated with the innate and adaptive immunity, that alone doesn't tell us that there is no inflammation present. That just tells us there is no increase in lymphocytes. Correct?
A. Again, I would have to look at his report. If you want to give me his report and the study. I don't feel comfortable commenting from memory on that.
Q. If one is looking for signs of inflammation and one says, I do not see an increased number of lymphocytes, but I don't report the number of macrophages, neutrophils, NK cells, and all the cells associated with the innate and adaptive process, all that tells you, there is not an increase in lymphocytes; it doesn't tell you there is not an increase in inflammation. Wouldn't you agree?
A. It doesn't say there is an increase in those other cell types. I'll agree with that.

Q. Did Dr. Shih have access to the medical records from the woman in which these slides came from?
A. I don't recall.
Q. That would be important; would it not?
A. Important for what?
Q. Well, if we are going to say there is no evidence of increased lymphocytosis, if there is no increase in lymphocytes, wouldn't one want to know if the patients from which they came had underlying medical conditions that were being treated with medications known to decrease lymphocyte counts?
A. Not if the question is whether there is any evidence or inflammatory cells in STICs. That's the question. He was asking whether in 43 cases that he saw of STICs or p53 signatures, if whether there was any indication of inflammation, and that's what the study was addressing.
Q. Limited to his observation of the number of lymphocytes?
A. As I said, I can't testify honestly to that without seeing the report.
Q. Let's assume for a moment the study was limited just to the presence of lymphocytes. He doesn't know if the patient from which that study came was on tegretol, which is known to cause decreased lymphocyte

counts. You don't know that, do you?
A. You would have to speculate a large number of the patients were on that because he looked at 43 cases.
Q. Of those 43 patients, we don't know how many of those patients had heartburn and were going across the street to take Tagamet, do we?
A. No.
Q. We don't know if any of them had a prior organ transplantation, and they were on organ rejection medication, which reduces the immune response. Correct?
A. Yes.
Q. And we also don't know how many of those STICs that he observed, that were devoid of evidence of inflammation around them, were actually metastatic cells from elsewhere, whether the Fallopian tube or anywhere else, because there is publication showing up to 25 percent of STIC are seen in the ovary are metastatic?
A. I'm extremely familiar with that publication, and you are misstating the evidence completely because those patients would have had ovarian cancer, and he discriminated in his study between patients with ovarian cancer and patients with STICs, and the STICs

he looked at were STICs from patients are without evidence of ovarian cancer.

Q. If you are familiar with that study, you know they did. And I'm going blank on the exact name of it -- is it genomic testing?

A. Genomic analysis, yes.

Q. It would tell you from whence in the body the cell came?

A. It's a paper by Lengyel, and he is a well known ovarian cancer researcher from Chicago, and that was studying whether some STICs were metastatic ovarian cancer cases. That was the study.

Q. I believe I'm referring to another. I want to ask you this:

Do you have an opinion as to whether or not some percentage of STICs that can be observed in the ovaries of women have actually come from elsewhere?

A. Yes. Can I elaborate? You are asking it completely out of context.

Q. If those STIC lesions came from elsewhere, we really don't know if inflammation caused those STIC elsewhere and they then migrated?

A. That's not what happens. I think you are misstating the way that things actually happen.

The studies that show some STICs can be

metastatic show that they come from a widely metastatic tumor. You wouldn't expect to see a STIC in a patient without a relatively obvious cancer and that patient would have been excluded from Dr. Shih's study.

Furthermore, there is no question that fully blown ovarian cancer is associated with inflammation; and, so, if anything, a metastatic STIC would be much more likely to have inflammation associated with it than not. So I don't accept the premise of your question.

Q. Do you know if Dr. Shih was unable to account how many of the STICs he observed came from elsewhere in the body?

A. As I tried to answer, he said these were from patients without ovarian cancer. So this was a study -- this study I'm pretty familiar with. It was a large scale study which our institution when I was in Canada at Princess Margaret Hospital participated in, and it collected a large number of samples from patients with ovarian cancer and other patients, and that was what the study was about. I think it was the DOD academy study.

MS. SHARKO: Your Honor, I think we are a little past the two-hour mark.

THE COURT: How much longer do you have?

MR. RESTAINO: How much longer are you going to give me?

THE COURT: We're a little earlier than yesterday. So I'll give you a little more time.

BY MR. RESTAINO:

Q. Doctor, the STICs are serous lesions?

A. Precursor lesions for high grade serous ovarian cancer but they are early lesions.

Q. Are they associated only with the high grade serous ovarian cancer?

A. Yes.

Q. Group 1?

A. Type II tumors.

Q. They are not what you would call the Group 1?

A. Correct.

Q. Do you agree a lack of inflammation with STIC tells us nothing about the pathogenesis of Group 1 ovarian cancer?

A. Can we use the term Type I.

Q. Let's talk about what you call Type I or ovarian cancers. These are primarily the high grade tumors. Correct?

A. No, exactly the opposite. Type II tumors are the high grade tumors. Type I tumors are more often

the ones that come from endometriosis.
Q. You would agree 60 percent and possibly all of the high grade serous ovarian cancers originate in the Fallopian tube?
A. I think you are quoting my report.
Q. Do you agree?
A. That's an example where I did consider both sides of the question. Actually, many ovarian cancer researchers are firmly convinced 100 percent of high grade serous cancers come from the Fallopian tube, and the evidence is still not that strong. That's why I couched that.
Q. If inflammation caused the initial mutation, wouldn't that inflammation be found in the Fallopian tube?
A. What do you mean "the initial mutation"?
Q. The inflammation that led to the DNA errors which leads to mutagenesis and carcinogenesis.
A. What's the question?
Q. If inflammation initiated this cascade leading to the Type II high grade which originated in the Fallopian tube, you would expect to see it in the Fallopian tube. Correct?
A. Yes.
Q. Did Dr. Shih look in the Fallopian tube?

A. Yes. He looked in STICs which are in the Fallopian tube, in the fimbria.
Q. For the remaining 40 percent where you wrote "no precursor lesion can be identified," so there is no specific site where scientists can even look for inflammation. Correct?
A. Again, I did write that, but in the context of your question, it is a little bit misleading. So, again, in the studies that have been done thus far, the studies look for synchronous lesions in patients with ovarian cancer and Fallopian tubes that were not completely involved in the cancer. And in those cases they could in 60 percent of the cases find a precursor lesion, a STIC, if you will, and they check to see whether the STIC had the same mutation or in some cases mutations as in the ovarian cancer. That doesn't really mean that there is no precursor lesion in the other 60 percent. It just means that, for example, the tumor was so developed that it encased the Fallopian tube and you couldn't find the original precursor lesion. That's what it means. Just to be clear.
THE COURT: Do your timing by 2:30, please.
MR. RESTAINO: Yes, your Honor, thank you.
BY MR. RESTAINO:

Q. Doctor, you testified this morning that p53 deactivation is the sine qua non of what you call Type II ovarian cancers which include the high grade. Is that correct?
A. p53 mutations is what I said. Some of the mutations are neomorphic activity, and they are inactivating p53 function, but they are interfering with two other tumor suppressors, and I was trying to make it simple because it is very complex.
Q. Doctor, the p53 gene, when it becomes mutated, is a oncogene?
A. P53 is generally termed the tumor suppressor gene.
Q. Mutated p53 is by definition --
A. That's an argument that one can have.
Q. But you indicate in your report Dr. Shih doesn't have a basic knowledge of biology because he called p53 an oncogene in his deposition, right?
A. It was the context he used the term. If you want to go to that part, I would show you why that's true.
THE COURT: Dr. Shih or Dr. Saed?
THE WITNESS: Dr. Saed?
A. You meant Dr. Saed.
Q. Dr. Saed. I apologize.

Now, if you were asked on direct examination about the Buz'Zard study?
A. Yes.
Q. You stated the paper was not consistent with Dr. Saed's data and conclusions?
A. That's correct. Not in detail. If you look in detail at the actual data.
Q. If you look at the Buz'Zard data they have the same dose of talc Dr. Saed found ROS that were actually lower than the treated cells in the controlled. Correct?
A. One of the doses they used was the same as Dr. Saed used, yes.
Q. If you look at the Buz'Zard scientists actually found -- if we looked at A 16, which is the Buz'Zard 2007.
A. Yes.
Q. Turning to page 5, Figure 3, the authors reported, "the ROS generation of ovarian epithelial cells, granular ovarian cells had the effects over time." Correct?
A. Yes.
Q. Their report results in the paragraph below. Correct?
A. Yes.

Q. And they write that "Talc caused an initial dose dependent decrease in ROS generation."

You stated that, correct, in your report. You discussed that?

A. I don't believe I expressed that detail in my report. I stated it this morning in response to Ms. Sharko's questions.

Q. Now, the talc caused an increase in ROS with time; did it not?

A. Can we actually look at the data instead of their statement? We just looked at the data. I'll be happy to point out my point. Let's look at the figure you put up.

Q. It is page 5, Figure 3.

A. If you look at the panel that says 100-microgram per mill dose, which is the dose Dr. Saed used 24 and 72 hours, which hours -- 72 hours is, I believe, the time of Dr. Saed's experiment, and you compare it to the 0., you will notice both at 24 hours of talc and 72 hours of talc, the ROS has measured directly by ECF staining, which is a standard assay for measuring ROS is decreased. That's what I said in response to Ms. Sharko's question this morning.

Q. It was decreased, but other times it was increased?

A. No. Every time point at a hundred it is decreased. Even at the 120 point.

Again, with respect, if I can clarify, this morning -- yesterday Dr. Saed said that you don't need to measure ROS levels directly. You can simply infer them or deduce them from measuring the level of pro and antioxidants in the cell. And I said that that wasn't true in my report. I think this is a good example of why what I said was accurate.

Furthermore, the statement that the Buz'Zard paper supports Dr. Saed's study is repudiated or questioned by this data, isn't it?

Q. It is not your opinion that over time these levels increased?

A. I don't think it is a matter of opinion. If you simply look at the data, you can see that in the 100 point, which is what Dr. Saed did, all time points in the study is reduced. That's not an opinion. That's data.

Q. Now, I want to finalize that some of your opinions and used examples of, that certain inflammatory disease are not associated with cancer?

A. I didn't say that.

Q. You didn't say rheumatoid arthritis is not associated with levels of cancer?

A. I said it wasn't clearly associated with ovarian cancer to my knowledge.
Q. I stand corrected. It is not associated with ovarian cancer. Rheumatoid arthritis is in fact an inflammatory arthritic condition. Correct?
A. Yes.
Q. And rheumatoid arthritis has been associated with other forms of cancer?
A. Perhaps I can't remember in detail whether that's true or not. I wouldn't be surprised, though. I'm not testifying as to that. I'm testifying as to ovarian cancer.
Q. However, it is the inflammatory effect that I'm focusing in on. It is associated with Hodgkin's and nonHodgkin's lymphoma, is it not?
A. Yes, but that's misleading in terms of the conclusion because Hodgkin's disease is a disease of the lymphocytes. So it is a little -- that's the innate and inactive immune system interacting. So it's not analogous to an epithelial cancer.
Q. You mentioned SLE in your expert report?
A. Correct.
Q. And you said it was not associated with ovarian cancer?
A. Not to my knowledge.

Q. And SLE is an auto inflammatory immune disease?
A. Yes.
Q. And SLE is in fact associated with other forms of cancer including nonHodgkin's lymphoma?
A. What you are saying is true, but it misstates the connections. But it is part of the immune system, so it is not surprising a frequently stimulated immune system may lead to an immune cancer.
Q. You write psoriatic arthritis is also not associated with ovarian cancer?
A. As far as I know, no.
Q. But the inflammatory process of psoriatic arthritis is associated with the development of cancer elsewhere?
A. Again, cancer is not one disease.
Q. And you also said NSAIDS, non-steroidals are not associated with a decrease in the incidence of ovarian cancer. Correct?
A. That's correct.
Q. The implication being if in fact ovarian cancer is caused by inflammation, individuals taking an NSAID, Aleve, would have a decreased incidence of ovarian cancer?
A. That was not my implication. That may be your inference.

Q. You state it is not associated with a decreased risk?
A. That's correct.
Q. And you put in several references?
A. Yes.
Q. Aspirin is a form of a non-steroidal anti-inflammatory drug. Correct?
A. That's correct.
Q. And aspirin is associated with a decreased risk of ovarian cancer?
A. That's a very complex issue which you reduced to a sound bite which is not exactly accurate. Can I elaborate?
Q. Sir, in the last minute I have, if you can look at PSC Neel 14. That's the associations between aspirin use and risk of cancer meta-analysis.
Q. Sir, in the abstract you can see this is a meta-analysis of observational studies.

"We have conducted an updated meta-analysis to assess the associations between aspirin use and cancers."

And under "results" 218 studies, you see "aspirin use was associated with a significant decrease in the risk of overall cancer, relative risk 0.89," and going down a couple of more lines,

"ovarian" with a relative risk of 0.89.

"These findings suggest that aspirin use is associated with a reduced of gastric, esophageal, colorectal, pancreatic, ovarian, endometrial, breast, and prostate cancers and small intestine neuroendocrine tumors."

A. Yes. But if you look in detail at the paper and the follow-up paper which was published in 2019, it shows the effect of aspirin is only for people who use it every day, and only over a certain time period, and not people who use it four times a week, and only at the lowest doses, and aspirin has other effects NSAIDs don't have.

In particular, low dose aspirin affects platelets, and platelets have an independent possible effect on ovarian cancer. So the fact that aspirin at low doses, given with very defined dosing intervals has an effect, does not really give you much information about inflammation in ovarian cancer, in my opinion.

Q. But the aspirin is shown in association with decrease risk of these studies and aspirin is a non-steroidal inflammatory drug?

A. Again, you are cherry-picking, in my opinion, a small piece of a study and trying to come to a general

conclusion. Your statement is, as stated, correct, but the implications are not correct in my opinion.

THE COURT: Thank you.

MR. RESTAINO: Thank you for your indulgence.

THE COURT: No problem.

MS. SHARKO: I have a very short redirect. Can I have five minutes?

THE COURT: Sure.

THE DEPUTY CLERK: All rise.

(Recess.)

(Continued on the next page.)

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THE DEPUTY CLERK: All rise.

THE COURT: Thank you.

BENJAMIN G. NEEL, resumed.

REDIRECT EXAMINATION

BY MS. SHARKO:

Q. Dr. Neel, let's take a look at Exhibit 16, the Reid paper that Mr. Restaino used on cross-examination.

First of all, is Reid a review article or is it an epi study?

A. It's a review article.

Q. Secondly, do you need to have biologic plausibility for a risk factor?

A. No.

Q. And what Mr. Restaino was discussing with you in connection with this paper were risk factors. Correct?

A. Yes.

Q. Now, if we could go to Table II of the exhibit.

Now, Dr. Neel, you asked several times or pointed several times to the idea of separating out risk factors based on subtype of ovarian cancer. Correct?

A. Yes.
Q. Does Table II on page 20 of the Reid paper in fact do that?
A. Yes.
Q. And, so, if we look across the top, it lists five subtypes of ovarian cancer. Correct?
A. Correct.
Q. Now, let's look at the left-hand column of the paper. There is a title there that is "established risk factor." Correct?
A. Yes.
Q. Please take a look at the established risk factors identified by Reid in his paper in the left-hand column. Do you see "talc use" there?
A. No.
Q. Now, let's go to Exhibit A 104, please.
Mr. Restaino asked you about the PDQ from the NCI for asbestos. Correct?
A. Yes.
Q. But there is a PDQ for ovarian cancer, isn't there?
A. Yes, there is.
Q. Let's take a look at what the PDQ for ovarian cancer says about perineal talc use on page 13.
It says:

"The weight of evidence does not support an association between perineal talc exposure and an increased risk of ovarian cancer."

Correct?

A. Correct.

MS. SHARKO: No more questions. Thank you.

THE COURT: Thank you. You are excused, Dr. Neel.

(Witness excused.)

THE DEPUTY CLERK: All rise.

(Court adjourned at 2:50 p.m.)

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I N D E X

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C E R T I F I C A T E

PURSUANT TO TITLE 28, U.S.C., SECTION 753, THE FOLLOWING TRANSCRIPT IS CERTIFIED TO BE AN ACCURATE TRANSCRIPTION OF MY STENOGRAPHIC NOTES IN THE ABOVE-ENTITLED MATTER.

S/Vincent Russoniello
Vincent Russoniello, CCR
Certificate No. 675

P